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COMMONWEALTH BUREAU OF ANIMAL HEALTH

VETERINARY REVIEWS AND ANNOTATIONS

Volume 2 **April, 1956** *Part 1*

The Treatment of Tapeworm Infestations in Man and Animals

BY

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The treatment of tapeworm infestations presents many difficulties and the drugs used for the purpose are far from perfect. The efficiency of many medicaments is low or variable and in some there is a narrow margin between the therapeutic and the toxic dose. The older anti-cestode drugs have been used by primitive peoples in different parts of the world for centuries. Areca nut, kamala and pomegranate originated in Asia, kousso in Africa, male fern in Europe and spigelia in North America. These and most, if not all, of the more recently developed drugs have been discovered empirically. The precise mode of action of most of the drugs is not known and the relationship between chemical structure or properties and anthelmintic activity has not been clarified. Only in a few instances have large series of related compounds been examined in attempts to find such a correlation.

In the past, anti-cestode drugs have been divided into two main categories, the taeniacides which kill the parasite in situ and the taeniafuges which cause the elimination of the living worm. From the practical point of view, the division is an unimportant one. Purgation alone has little, if any, effect on tapeworms but taeniafuges which usually cause purgation or are combined with purgative drugs have, in addition, a direct effect on the nervous or muscular system of the parasite and only worms so affected are removed by the treatment.

In this review an attempt is made to summarize the present position in regard to man, domestic animals and birds. Methods of investigation most suited to the evaluation of taeniacidal drugs are discussed. The review covers the period up to the end of 1954, and throughout, emphasis is placed on experimental rather than clinical studies, except where the latter provide information on points not covered by the former.

TECHNIQUES OF INVESTIGATION

IN VITRO TECHNIQUES

In vitro techniques have been used by a number of workers studying the cestodes. Apparently, the first of these was Schroeder in 1884, who placed specimens of Taenia from the cat in a solution of pelletierine and found that all movements ceased. It appears that kymographic methods were first used by the Portuguese school, Rebello et al. (1928) using T. serrata and Dipylidium caninum. More recently Batham (1946) has used Taenia from dogs and Duguid & Heathcote (1950) Moniezia from sheep. The use of earthworm or leech material to study anthelmintics has been condemned by several workers, notably Rebello, Baldwin and Duguid & Heathcote, because of the wide differences in response between cestode, nematode and annelid preparations.

Kymographic studies can be carried out on individual segments of Taenia species or with short chains in cases such as Moniezia. The material may be obtained as segments, freshly evacuated in the faeces or as entire parasites obtained after the slaughter of the host or removed by a taeniafuge such as arecoline. Use might also be made of Taenia taeniaeformis or its larval stage, the strobilocercus from the liver of rats and mice. The latter may have special value in that it is robust enough to stand manipulation while retaining its scolex and therefore the nerve ganglia, which would be absent from the strobila or from individual segments.

Preparations such as these may retain their activity for several hours when immersed at 37°-40° C. in isotonic solutions such as physiological saline, Ringer, or Tyrode solution. Rebello used Rhode & Saito's solution at pH 6.4 but Duguid & Heathcote found that this medium appeared to reduce the activity of some drugs, particularly the alkaloids. Kymographic tracings clearly record reactions such as stimulation, shown in increased frequency and amplitude of the contractions or an increase in the general tone of the musculature, depression shown by a decreased frequency or amplitude of contraction, even to complete paralysis, or a decrease in general tone. Duguid & Heathcote have pointed out that in many cases the paralysis is only temporary and this should always be tested by washing out the test drug and adding fresh medium and a stimulant such as strychnine, sparteine or hexylresorcinol or if the preparation is suspended in a tonic contraction, a paralysant such as arecoline should be added.

Ross (1927) has studied the effect of four substances, acriflavine,

tartar emetic, emetine and trypanblue in vitro on the brood capsules of Echinococcus granulosus. Their toxicity was in the order named but all were much less toxic than formaldehyde or mercury perchloride studied by Coutelen (1927). The technique used by Ross was to obtain scolices from hepatic or pulmonary cysts under aseptic conditions; scolices were then added to serial dilutions of the test drug dissolved in normal saline and the tubes, incubated at 35°C., were kept under observation for 48 hours. The lethal time was determined by pipetting off small quantities at intervals and examining them on a warm stage at 39°C. and noting changes in motility or structure. Ross's work was directed towards the possible use of medicaments against the somatic stage of the hydatid parasite but the same technique, no doubt, could be used to study taeniacides in general. For this purpose, the brood capsule could provide a useful screening organism but its potentialities for this purpose have never been seriously exploited.

IN VIVO TECHNIQUES

Holten (1947) described a biological assay technique for taeniacides using mice naturally infested with Hymenolepis. The test was illustrated with data obtained with extract of male fern. The mice were fed on sugar for 15 hours before treatment and a purge of 1 ml. 6.5 per cent wt./vol. magnesium sulphate was given by stomach tube 2 hours after treatment. Dose rates of 1.25-10 mg. extract given as a 5 per cent emulsion, were used. The mice were all killed 5 hours after dosing and the effect of the dose determined from the ratio of wet weight of worms affected by the drug, i. e., those passed, those found in the large intestine and dead worms found in the small intestine, to the total worms present. The wet weight rather than the number of worms passed, was used by Holten because of the difficulty of finding the delicate scolex of Hymenolepis. The mice used were infested with both H. nana and H. diminuta but using total weight as the criterion, the smaller H. nana contributed little to the final figure. The probits of the percentage wet weight of worms affected increased in linear relation to the logarithm of the dose. Holten considered that 15 mice per group were necessary in tests of this nature.

In experiments with more or less delicate parasites of poultry, the techniques used by the American workers appear to be the most satisfactory. Harwood & Guthrie (1940) described a test in which fowls were artificially infested with a number of cysticercoids dissected from the intermediate host, Tribolium, in the case of Raillietina cesticillus or Orthophagus hecate in the case of Hymenolepis carioca. The birds were treated 2-4 weeks later after fasting them for 18-24 hours. The faeces were collected after treatment and the uninfested birds discarded. The birds were held for a further 2 weeks before autopsy to allow regeneration of the strobila from a retained scolex. Starvation before slaughter should be avoided because of the destrobilization that may occur in fasting birds. Kerr (1948) modified this test slightly in that he used naturally infested birds or infested them artificially with about 75 cysticercoids per bird in unopened beetles. The infestation rate in the beetles was estimated by

the dissection of about 40 beetles in each batch. Untreated control birds were examined in all these tests.

CRITICAL TEST

The critical test devised by Hall has been used by a number of investigators but it cannot be used with parasites that are delicate and tend to disintegrate in the intestine nor can it be used with taeniacides such as dichlorophen which is reputed to cause death and rapid disintegration of the parasites. It has been used satisfactorily, however, with Taenia, Dipylidium and Echinococcus. The faeces passed after treatment were screened and the number of scolices passed recorded. Later the animal was killed and the number of scolices remaining indicated the percentage efficiency. The accuracy of the test is open to some criticism in that some worms passed may not be recognized. Penfold (1936) working with T. saginata, produced evidence that in some cases the patient may have been cured even though no scolex was recovered even after a careful search of the faeces passed after treatment. He also pointed out that a cure could occur even without the passage of large lengths of strobila and assumed that it was digested. In a series of tests made by Batham (1946) on Echinococcus, artificially infested dogs were used. After a period of 7-10 weeks they were dosed with arecoline hydrobromide. After treatment the faeces were collected, screened and the worms passed were counted individually or by dilution. The next day the dogs were killed and the worms remaining in the intestine were counted in the same manner.

Harwood & Jerstad (1938) devised a critical test for use with R. cesticillus in poultry, in which a number of birds were each given a single cysticercoid, the birds being kept under conditions in which accidental infestation was impossible. Twenty days after infection, those birds found to be passing segments were known to be infested with a single worm. Infested birds were then treated and killed a week later.

The critical test has been modified by Enzie et al. (1953) working with Moniezia expansa in sheep. They measured the volume of segments passed 1-3 days before and 3 days after treatment with dichlorophen, and recorded the volume and number of scolices remaining in the host on slaughter. They found that Moniezia did not disintegrate after treatment with dichlorophen.

STANDARDIZED TEST TREATMENT

The standardized test treatment has been used by Darling & Smillie (1921) in their studies on human hookworm. Human subjects were used in the original study. The test drug was given to a series of infected cases and the worms passed after treatment were counted. Subsequently a full dose of a drug of known efficiency was given and again the worms passed were counted and therefore represented those not removed by the first treatment. The same test is applicable to tapeworm studies and Whitten (1951) has used it in a modified form with Echinococcus in dogs. In this

case, no attempt was made to count the worms passed after dichlorophen because of possible degeneration, but those remaining were estimated following a dose of an arecoline salt. In this instance the number of failures was recorded rather than an estimate of the percentage of efficiency.

PHARMACOLOGICAL CONSIDERATIONS

There are relatively few papers published on the pharmacological action of drugs on cestode preparations. The most important are those of the Portuguese School (Rebello et al., 1928, 1933) and more recent ones by Duguid & Heathcote (1950). The latter authors in their two papers have considered the anthelmintic and non-anthelmintic drugs separately. On the basis of in vitro tests, they divided the anthelmintics into the following categories.

Inactive:
Santonin; Phenothiazine; Pseudopelletierine.

Depressant:
1-Pelletierine; Methylisopelletierine; Arecoline.

Stimulant:
Gentian violet.

Stimulant followed by depression but not lethal:
Male fern; Carbon tetrachloride; Tetrachlorethylene; Betanaphthol.

Stimulant followed by depression and death:
Oil of chenopodium; Thymol; Hexylresorcinol.

From the results of their experiments, Duguid & Heathcote made the following suggestions. As pelletierine tannate contains up to 50 per cent pseudopelletierine, a substance which is somewhat toxic to the host but inert against the worms, its elimination from official preparations might be advantageous. The effect of the alkaloidal drugs appeared to be influenced by the pH of the medium and the use of antacids with such anthelmintics may be advisable. As atropine did not interfere with the action of arecoline on the worm it might be used as an antidote with little fear of it reducing efficiency. (This would, of course, reduce the cathartic action of the drug on the host which may in itself affect efficiency).

In their second paper they examined over 40 drugs which are not nornormally used as anthelmintics. These they divided into four groups:

A. Little or no activity, i.e. no effect below 1:1000
Phloroglucin, pilocarpine, carbachol, atropine, posterior pituitary extract, tetraethylammonium iodide, alpha-picoline, methyl iodide, ethyl

alcohol, tetramethylammonium iodide, bile salts, 4:4'dipyridyl and 4:4'-dipiperidyl.

B. Drugs with slight activity 1:1000 - 1:10,000

Tyramine, adrenaline, amphetamine, cocaine, physostigmine, aconitine, caffeine, pyridine, alpha-pipecoline, barium and magnesium salts.

C. Drugs with moderate activity 1:10,000 - 1:100,000

2-methyl pyridine, 2:6-dimethylpyridine, 2:4:6-trimethyl pyridine, piperidine, 2:6-dimethylpiperidine, 2:4:6-trimethylpiperidine, nicotine, sparteine, morphine, codeine, thebaine, papaverine, ephedrine, veratrine and alpha-naphthol.

D. Drugs with high activity Over 1:100,000

Camphor, menthol, emetine, cephaeline, strychnine, brucine, acetylcholine, quinine and coniine.

The varying response of cestode material to related drugs was rather striking; of the drugs which are cholinergic in the mammal, carbachol and pilocarpine were inert, acetylcholine was depressant at 1:200,000 and arecoline depressant at 1:10,000,000. As the effect was not antagonized by atropine there can be no cholinergic receptors as seen in mammals. Of four drugs that are sympathomimetic in mammals, adrenaline was depressant in cestodes while ephedrine, tyramine and amphetamine were all stimulant. In cestodes there is no evidence of adrenergic receptors like those seen in mammals. As was expected, drugs of the nicotine group acted differently since there were no nerve cells in the preparations used in these experiments. Tetraethyl- and tetramethyl-ammonium iodide were inert, nicotine weakly depressant, coniine strongly depressant, sparteine moderately stimulant and piperidine stimulant and then depressant. In mammals, morphine, codeine and thebaine all stimulate smooth muscle but in cestodes morphine was stimulant while codeine and thebaine were depressant. Emetine and cephaeline produced strong stimulation and a tonic contraction that was permanent, an effect not unlike rigor mortis as seen in striated but not in smooth muscle of vertebrates.

ANTI-CESTODE DRUGS

A logical classification of the substances having anti-cestode activity is difficult but the following is a rough arbitrary grouping of materials for which activity has been reported. The names used are usually those in the British or United States Pharmacopoeias or the British Veterinary Codex. Trade names have been avoided except in a few instances where they have been used with inverted commas, for the sake of brevity. Many of the materials listed cannot be recommended because of their weak or doubtful action or because of toxic hazards.

Materials with Anti-Cestode Activity in vivo

MATERIALS OF PLANT ORIGIN

Phlorglucinol derivatives

Filicic acid (extract of male fern); Rottlerin (kamala); Kosotoxin (kousso, koso, cusso).

Alkaloids and their salts

Arecoline hydrobromide; Arecoline-acetarsol; Pelletierine; Methylisopelletierine; Spigeline; Conessine.

Proteolytic enzymes

Ficin; Raigan; Mexicana.

Miscellaneous

Ascaridol; Thymol; Pumpkin seeds; Sargassum; Dianthus.

INORGANIC AND METALLO-ORGANIC COMPOUNDS

Inorganic compounds

Lead arsenate; Copper sulphate; Arsenious sulphide; Ferric arsenate; Iodine; "Stannoxyl".

Metallo-organic compounds

Di-n-butyl tin dilaurate; "Anthelin"; Tin oleate; Tin tartrate; Tin oxalate; Tin maleate; Phenylmercuric phthalate.

SYNTHETIC ORGANIC COMPOUNDS

Dyestuffs

Brilliant green; Malachite green; Gentian violet; Basic fuchsin; Methyl green; Alizarin; Aminacrine hydrochloride.

Halogenated aromatic compounds

Mepacrine hydrochloride; Chloroquin phosphate; Dichlorophen; Hexachlorophene; "Tenamid"; Tertiobutylchlorobetanaphthol; Bis-(5-chloro-2-hydroxyphenyl) sulphone.

Miscellaneous

Carbon tetrachloride; Tetrachlorethylene; Hexylresorcinol; Isoamylorthocresol; Perthiocyanic acid.

MIXTURES

Copper and nicotine sulphates; Tin oleate and pelletierine tannate; Tin oxalate and pelletierine tannate; Tin tartrate and pelletierine tannate; Tetra-isobutyl tin and pelletierine hydrochloride; Tin oleate and triethanolamine; Tin oleate and ammonium hydroxide.

SPECIFIC TREATMENTS

MAN

Tapeworm remedies that have been in use for very many years include preparations of kamala, kousso and spigelia, the active principles being respectively, rottlerin, kosotoxin and spigelin. Chopra & Chandler (1928) have discussed them in some detail. Pomegranate bark has also been used extensively and its alkaloid is still official as pelletierine tartrate in both the British and United States Pharmacopoeias. It should be used only in adults.

Taenia saginata and *T. solium*

Male fern

Male fern for many years has been the drug of choice in the treatment of taeniasis in man. Extract Felicis mas (B. P.) and Oleoresin of Aspidium (U. S. P.) both contain approximately 25 per cent of crude filicic acid; the recommended dose rates are therefore 3-6 ml. for the former and 4 g. for the latter. Because of the rather narrow margin between the therapeutic and toxic dose it is important to prepare the patient adequately before treatment; the alimentary tract should be as empty as possible to expose the worm to the action of the drug. Light diets followed by overnight starvation with thorough evacuation of the bowels before treatment are recommended. It is preferable for treatment to be given in hospital so that adequate preparation can be assured. The drug is usually given in the morning and the patient kept in bed to minimize nausea. After 2 hours a saline purgative is given to sweep the drug and the parasites out of the intestine. If no worm is passed an enema or another purge is given. Treatment should not be repeated within 7 days.

Penfold (1936) has treated 86 cases and 77 were cured with the first treatment. Patients in which treatment failed on the first occasion were retreated with good results, at least eight and possibly nine out of the nine being cured. He considered therefore that one failure did not justify changing the drug. The doses of extract recommended by Penfold were rather higher than usual, being 10.7 ml. for adults over 66 kg., 8.8 ml. for those 56.5 - 66 kg. and 7.1 ml. for those weighing 44.0 - 56.6 kg. Penfold considered that if the scolex was not found retreatment should not be given unless segments reappeared, as sometimes cures were achieved even though the head was not recovered. The patient was considered to be cured only if no segments appeared for 100 days after treatment. Several workers have recommended the administration of the drug through a duodenal tube so that the drug reaches the worm at maximum strength.

Carbon tetrachloride

Sandground (1938) and Mukerji & Maplestone (1943) claimed that the efficiency of carbon tetrachloride against *Taenia* was 70-80 per cent but that this remedy was probably more toxic than male fern. The safer anthelmintics tetrachlorethylene and hexylresorcinol were less

effective, removing only about 50 per cent of the tapeworms present.

Pumpkin seeds

Pumpkin seeds have been a household remedy for tapeworms for many years though most investigators agreed that they were less effective than male fern. It has been considered that the effect was a mechanical one due to the sharp edges of the bruised seed (Chopra & Chandler, 1928). The usual dose was 30 - 40 g., and sometimes up to 100 g. but Krayer (1937) claimed that massive doses of 400 - 700 g. were effective if followed by a purgative. He claimed that the active principle was mainly in the kernel and was absent from the oil. It could be extracted from the seeds by boiling water.

Raigan (Omphalia lapidescens)

Terada & Sai-Ryo (1938) studied raigan, a Chinese remedy made from the powdered fungus and given in doses of 0.3 g. three times daily for 3 days. It contained a proteolytic enzyme which digested the tapeworm. It was non-toxic and no purgatives were necessary.

Tin compounds

Several workers used "stannoxyl", a mixture of metallic tin, tin oxide and tin salts. It was preceded and followed by a purge. Basnuevo (1948) recorded 60 per cent and Hirte (1951) 98 per cent efficiency. Le Gac (1947) found the drug effective against both *T. saginata* and *T. solium*. It was non-toxic.

"Tenamid" = Beta-(4-hydroxy-3, 5-diiodophenyl) alpha phenyl propionic acid
= Beta-phenyl-beta-carboxy-alpha (3,5-diiodo-4-hydroxy phenyl) ethane

"Tenamid" which was developed by Schering Corporation has shown a high degree of efficiency (50 - 90 per cent) against the Taeniidae in man; (Valencia Parparcen, 1947; Costa, 1949). No special diet or purgatives were necessary and there were no side effects. The dose recommended was 6 g. for adults.

Tertiobutyl-6-chloro-1-betanaphthol

Crismer & Dallemagne (1951) used the above compound in 5 g. doses, given 0.5 g. every 5 minutes and followed after an hour by a purgative. It cured about 90 per cent of cases. It was non-toxic to man and dogs.

Acridines

Mepacrine hydrochloride was first used against *T. saginata* in man by Neghme (1940) and over the past decade or so numerous papers have been published on its use against the tapeworms of man. The dose recommended was 0.8 g. for adults and it was usually given in 4 doses at 5-10 minute intervals, with 6 g. sodium bicarbonate. It was given after

fasting and followed after 2-3 hours by a saline or oily purge. Sometimes nausea and vomiting occurred but this was easy to control. The worms were stained yellow and were alive when passed. The efficiency against the Taeniidae was between 80 and 90 per cent.

Chloroquin phosphate

Chloroquin phosphate at a dose rate of 25 mg./kg. gave good results against T. saginata and was without toxic symptoms (Arteaga Camero, 1951).

Diphyllobothrium latum

Male fern

The efficiency of male fern against the broad fish tapeworm of man was reasonably high. Summers & Weinstein (1943) used it successfully in two children in Florida from whom 33 scolices were recovered.

Carbon tetrachloride

Several authors recommended caroon tetrachloride for the treatment of D. latum (Belding, 1942; Craig & Faust, 1945).

Thymol

Vartiainen (1950) considered that thymol, though it was ineffective against T. saginata, was the drug of choice against D. latum. On the other hand, p-cymene was ineffective.

Acridines

There is little information on the value of acridines against D. latum, but Ruikka (1951) treated 50 cases with mepacrine and found that 20 out of the 32 cases they were able to re-examine 5-20 weeks later, were free. The drug was well tolerated and he preferred it to male fern especially in old patients or those with heart disease.

Hymenolepis nana

Male fern

The results with male fern against H. nana were less satisfactory than against the larger Taeniidae. A number of Russian workers recorded percentage cures ranging from 26 for single doses to 62 when the dose was repeated at 10—15-day intervals to remove the worms present in the intestinal villi at the time of the first treatment. (Pod'yapol'skaia & Vassilkova, 1934; Podyapolskaya & Isaicheva, 1944; and Berkhina & Mukvoz, 1943).

Dyestuffs

Gentian violet Maplestone & Mukerji (1939) considered that gentian violet was a useful drug against H. nana. If given continuously for 6-7 days, it caused nausea and vomiting but this could be avoided without loss of efficiency by an interrupted course of treatment. Repeated courses of treatment were necessary to destroy the worms as they leave

the villi.

Acridines Shapiro (1951) considered that mepacrine was relatively ineffective against H. nana. Beaver & Sodeman (1952) on the other hand, found it highly effective, but a single dose failed to eradicate the infection.

Raigan (O. lapidescens)

The ground fungus and the extracted active principle have been found by Hiyeda & Terada (1939) to be effective against both H. nana and H. diminuta.

"Tenamid"

Valencia Parparcen (1947) used "tenamid" successfully against H. nana.

DOGS

Taenia and Dipylidium

Chopra & Chandler (1928) discussed the use of the older anthelmintic drugs including male fern, kousso, kamala, areca nut and pelletierine tartrate. These materials have been superseded and now are seldom used.

Arecoline hydrobromide

Arecoline is the active principle of areca nut but as the nut should be freshly ground and its arecoline content is somewhat variable, it is preferable to use a salt of the alkaloid, and the hydrobromide is the one usually chosen. It was apparently first used for tapeworms in dogs by Lentz (1921) and critical tests were made with the drug by Hall & Shillinger (1923) and by Ross (1924). Batham (1946) in her experiments with Echinococcus made observations on the efficiency of arecoline against the larger tapeworms, Taenia, Multiceps and Dipylidium. The percentage of worms removed was 90-100. For the best results, dogs should be kept on a light diet for a day before dosing; if constipated, preliminary purgation should be given. They should be dosed on an empty stomach. Evacuation of the intestine usually occurs in 15-45 minutes but if it does not occur within 2 hours, an enema should be given. The purpose of the enema is to bring about evacuation so that the worms, which are only paralysed, are removed. It is considered to be necessary as worms may recover and reattach. The importance of this is uncertain but there is a case on record from Wallaceville of a dog infested with Taenia which was dosed with arecoline hydrobromide. It vomited 10 minutes after dosing, but failed to purge. Eighteen hours later it was given a small enema and passed 6 specimens of Taenia, all of which were alive, 3 being complete with scolex while the other 3 showed degeneration, due no doubt to their sojourn in the lower bowel. These were still weakly motile, but the anterior ends were macerated and the scolices were missing. No tapeworms remained when the dog was killed 5 weeks later. It is usually considered that to give the best results the dogs should not vomit after dosing, and sedatives have been recommended

for this purpose. Provided vomiting does not occur within 5-10 minutes of dosing, the action of the drug is little impaired. It is sufficient to tie the dog up on a short chain so that it is more difficult for it to vomit, or to pet it or give it mild exercise for some minutes after dosing. There is a wide safety factor with arecoline and the toxic dose has been estimated to be from 8-30 times the medicinal dose. The antidote for arecoline is atropine, but it has no effect in antagonizing the paralysant action of arecoline on the cestode. The doses of arecoline hydrobromide usually recommended are 1-2 mg./kg., and the safety of this dose rate has been confirmed by many workers. Reinhardt (1933) used it on 1,000 dogs with good results, and in New Zealand, Miller (unpublished) has dosed over 8,000 dogs and experienced no losses that could be attributed to its use. Arecoline may be given with a little sugar to disguise the taste (Ferro, 1948). It is contraindicated in pregnancy. When administered parenterally it is of no value against tapeworms.

Arecoline-acetarsol

This organic salt of arecoline has been used widely in veterinary practice. It is recommended that arecoline-acetarsol should be given 3 hours after a light meal. The published reports on this compound indicate that its efficiency is similar to that of arecoline hydrobromide. It is difficult to see what advantage this compound has over arecoline hydrobromide as they both hydrolyse in the stomach and release arecoline, which is the active moiety. Acetarsol has negligible anti-cestode activity.

Tin compounds

Lepinay (1933) used tin oxide against tapeworms in dogs, with good results. Le Gac (1947) used "stannoxyl" successfully against *Dipylidium*.

Proteolytic enzymes

Hiyeda & Terada (1939) found raigan (*O. lapidescens*) effective against *D. caninum*.

Calderón Rodríguez (1949) compared preparations of *Pileus mexicana* and *Ficus glabrata*, by both *in vitro* methods and *in vivo* experiments with dogs and cats. Both materials were effective in removing *Taenia*.

Isoamylorthocresol

Stewart (1937) used 0.2 ml./kg. followed by magnesium sulphate, in 34 dogs. He claimed that it was effective against *D. caninum* but ineffective against *T. seriata* [*serrata*], *T. marginata* or *D. sexacoronatum*. Jerstad (1939) tested it in 12 dogs and found that it was quite ineffective against *D. caninum* and *T. pisiformis*.

Dyestuffs

Deschiens (1944) stated that the triamine dyes, basic fuchsin, and methyl violet, have a greater activity against *Dipylidium* than the diamines, malachite green, methyl green and brilliant green.

Perthiocyanic acid

Enzie (1944) used perthiocyanic acid at 200 mg./kg. with a maximum dose of 5 g. It was given without fasting and was followed by a saline purgative. It was highly effective but there was only a small margin of safety.

Dichlorophen = 2:2'-dihydroxy-5:5'-dichlorodiphenyl methane

Craige & Kleckner (1946) first used this material at 200 mg./kg. and these results were confirmed by Brinker & Platt (1946). The tapeworms were killed in the gut and digested. The material was not very toxic, vomiting was rare but a copious bowel movement often occurred 4-8 hours after dosing. The large dosage of the drug is a disadvantage especially when large dogs are to be treated with 0.5-g. tablets.

Acridines

A few papers have been published on the use of mepacrine against *Taenia* and *Dipylidium* in dogs. The dose rate was 15 mg./kg. after 12 hours' fasting followed by an oily or saline purgative. Sedatives were sometimes given to control vomiting. Link & Smith (1954) reported good results using 20-40 mg./kg.

"Anthelin" (N-methyltetrahydromethylnicotinate-p-carboxyphenyl stibonic acid)

Kartsonis & Austin (1950) used "anthelin" at a dose rate of 10 mg./kg. It was 97 per cent effective against *Taenia* and *Dipylidium*. Of 38 dogs treated, 92 per cent were freed from tapeworms and only 9 per cent manifested nausea. There was good tolerance to a double dose on three successive days.

Bis-(5-chloro-2-hydroxyphenyl) sulphone

Foster (1953) mentioned that this compound showed promise as a taeniacide in dogs, but as yet no experimental results have appeared in the literature.

Echinococcus granulosus

Arecoline salts

Ross (1927) treated four artificially infested dogs with arecoline hydrobromide and found that the efficiency was 98-100 per cent. In contrast, the treatment of one dog with extract of male fern yielded poor results. The same author (1936) used arecoline-acetarsol in one dog and reported that many worms were passed without the scolex. When the dog was killed, 3,100 out of 20,000 worms remained. He considered therefore that the drug was inferior to the hydrobromide. It is doubtful whether this conclusion was justified, as a figure of 85 per cent, while abnormally low, might reasonably be expected with a single treatment with either remedy.

A larger series of critical tests with arecoline hydrobromide against *Echinococcus* was reported by Batham (1946). She used 157 dogs that

were artificially infested and treated with doses ranging from 0.2 mg./kg. to 25 mg./kg. The median efficiency for doses over 0.4 mg./kg. was 95 per cent or more. Increasing the dose over 3 mg./kg. did not markedly increase the efficiency but it increased the proportion of dogs that vomited or had convulsions. The dose recommended in New Zealand is 1 mg./kg. but half or double this dose was equally satisfactory. When the drug was given in a piece of meat, it was almost as efficient as in water but its action was slower, purgation usually occurring after more than an hour instead of 15-30 minutes. From the repeated treatment of 16 infestations it was concluded that most dogs would be completely freed from infection after three doses, provided purgation followed. Half of the dogs were negative after two such doses, but in two instances a few worms were still present after five doses. Usually only very few worms were left after a single dose, but there were two exceptions in which the first dose removed only 10 and 16 per cent respectively.

The subcutaneous injection of arecoline produces purgation but has negligible anthelmintic action.

Dichlorophen

Whitten (1951) found that this drug failed to bring about complete removal of Echinococcus in several dogs. Results were checked later either by treatment with arecoline salts or by slaughter of the dog. Later unpublished work has confirmed this finding, 6,000 worms surviving treatment in one animal.

Recently a number of small-scale tests have been made at Wallaceville in the treatment of Echinococcus with the following materials (Whitten, unpublished):-

Acridines

Mepacrine hydrochloride failed to give satisfactory control of Echinococcus at 50 mg./kg. followed by either a saline or an oily purgative. Four artificially infested dogs slaughtered after treatment harboured 250, 3,500, 4,700 and 12,000 worms.

Lead arsenate

In view of the good results obtained with this compound in ruminants, it was tried in artificially infested dogs at a dose of 250 mg./kg. but with poor results.

"Tenamid"

"Tenamid" has also been tested in two dogs at 200 mg./kg. followed the next morning by a saline purge. The treatment was unsatisfactory, 12,000 and 20,000 worms remaining after treatment.

Perthiocyanic acid

Perthiocyanic acid at 50 mg./kg. has been tested in a small number of dogs, but the results have been disappointing.

Acetarsol

Acetarsol at 25 mg./kg. was not effective when tested on one dog.

"Anthelin"

At a dose rate of 10-20 mg./kg. "anthelin" shows promise of being a useful drug against Echinococcus. In three animals 100 per cent of 1,400, 9,500 and 25,000 worms respectively were eliminated after treatment. At 20 mg./kg. nausea, vomiting and the passing of bloody stools were fairly common.

Diphyllobothrium latum

Kamala

Rho (1934) used kamala successfully in treating D. latum infestation in a dog.

Arecoline hydrobromide

Gordon (1939) used arecoline hydrobromide successfully against D. latum in dogs. His experience emphasizes that care should be taken to see that the scolex is passed. In one of his cases, retreatment was necessary when segments reappeared in the faeces, presumably from scolices which were not removed.

Mesocestoides

It has been stated by Palimpsestow & Djegterenko (1935) that arecoline even at a dose rate of 4-15 mg./kg. was ineffective against Mesocestoides in dogs. Antipin (1946) found that arecoline and kamala were both inferior to male fern in treating Mesocestoides in raccoon dogs (Nyctereutes species).

CATS

Taenia and Dipylidium

Male fern, kamala and kousso have all been recommended for tapeworms in cats, but there is little published experimental work on their efficacy.

Arecoline hydrobromide

Arecoline hydrobromide is usually considered to be unsafe for cats because of the outpouring of bronchial secretion that the drug causes, which may result in suffocation. Feng et al. (1949) prepared a bismuth iodide compound of the alkaloid which they stated was effective against both Taenia and Dipylidium. Stephenson & Milks (1937) recommended freshly ground areca nut (0.5—1.0 g.) after 12-18 hours' fasting.

Arecoline-acetarsol

Arecoline-acetarsol has frequently been recommended for cats at the dose rate of 9 mg., three hours after a light meal. It is

not recommended for cats under 12 months of age.

Dichlorophen

Dichlorophen was used successfully in cats by Burch & Blair (1950) at 100-200 mg./kg. The drug was relatively non-toxic.

Acridines

Aminacrine hydrochloride was tested for cats by Tareeva (1953) at 200 mg./kg. It was effective against tapeworms at this dose rate and had a wide margin of safety.

Other materials

Reports have suggested that anti-cestode principles were present in Sargassum thunbergii (Go, 1940) and Dianthus spp. (Sitowski, 1937) but further confirmation is necessary.

SHEEP

Moniezia expansa

Copper sulphate

Copper sulphate has been used in the past for Moniezia infestation and it still appears to be popular among Russian workers, who use 1-2 per cent solution which may or may not be followed by magnesium sulphate. Gordon (1935) found that copper sulphate in solution was effective in one sheep out of two.

Copper sulphate and nicotine sulphate

This mixture has been popular for the treatment of sheep infested with Moniezia. It has been recommended by Freeborn & Berry (1934) and by Ross & Gordon (1936).

Arsenious sulphide

Gordon (1935) found that arsenious sulphide given as a powder or suspended in copper sulphate solution was highly effective in doses of 0.5 g.

Lead arsenate

McCulloch & McCoy (1941) found that doses of 0.5-1.0 g. for yearling animals were effective and safe, and this has since been confirmed by a number of workers in the U. S. A. Foster (1953) has recently indicated that ferric arsenate also shows promise against Moniezia.

Dichlorophen

Ryff et al. (1949) used dichlorophen in 10-g. doses in a small number of sheep and found it effective against Moniezia. In a later paper Ryff et al. (1950) reported that doses as low as 0.08 mg./kg. were effective. Enzie et al. (1953) on the other hand, using doses of 4.5 -15 g., found that it was only partially effective.

Thysanosoma actinioides

A number of remedies such as male fern, copper sulphate, and nicotine sulphate, have been used against Thysanosoma. Olsen & Allen (1945) tested carbon tetrachloride, tetrachlorethylene and hexachlorethane and found that they were ineffective. It has been suggested that some drugs are effective against the worms in the intestine but ineffective against those in the bile ducts (Harshfield & Esplin, 1943).

Dichlorophen

Ryff et al. (1949) reported that 10-g. doses removed Thysanosoma and reduced the percentage of livers condemned on account of infestation. Olsen (1953) also found a reduction in liver condemnations but concluded that the effect of the drug was too variable to be economically worthwhile. In all reports of the American experiments with dichlorophen, the drug has been given as a watery suspension or as tablets or capsules. The possible improvement that might follow if the drug were taken to the abomasum, by a preliminary dose of copper sulphate, does not seem to have been considered. This may explain the erratic nature of the response.

Lead arsenate

Only limited tests have been made with lead arsenate on sheep infested with Thysanosoma. Habermann & Carson (1946) found that it was ineffective in 1.0-g. doses, as did also Ryff et al. (1949).

CATTLE

Moniezia

Lead arsenate

American workers (Radeleff, 1944; Foster & Habermann, 1948; and Link et al., 1950) reported that lead arsenate was apparently effective in the treatment of Moniezia infestation in cattle.

POULTRY

The treatment of poultry cestodes has not been very satisfactory and it is only within recent years that there have been any drugs that could be recommended with confidence. Kamala, iodine and arecoline have been used, but careful tests have shown that their efficacy is low. Kamala frequently failed to remove scolices.

Raillietina

Dyestuffs

Wright (1937) showed by critical tests that brilliant green given in single doses was effective against Raillietina.

Lead arsenate

Harwood & Guthrie (1940) found that lead arsenate was

effective but too toxic for general use in poultry.

Tin compounds

Guthrie & Harwood (1941) reported that stannous oleate, tartrate, and oxalate were effective against R. cesticillus especially when combined with pelletierine. Guthrie & Harwood (1941) tested tetraisobutyl tin against R. cesticillus and found it ineffective, but in 1-ml. doses combined with pelletierine it was 100 per cent effective in an experiment with 10 birds. Larger doses were rather toxic. Guthrie & Harwood (1944) later found that tin oleate and triethanolamine was a useful taeniacide but it was unstable. Tin oleate and ammonium hydroxide was not effective against Raillietina. Kerr & Walde (1951) tested over 50 tetravalent tin compounds of the general formula

$$R_{4-n}\ Sn\ X_n$$

where R = alkyl, aryl or aralkyl

X = oxygen, sulphur or acid radicle, organic or inorganic

n = 1, 2, or 3.

Many of the compounds were effective against R. cesticillus. In 1952, Kerr reported favourably on di-n-butyl tin dilaurate. It can be given either in capsules at a minimum dose rate of 75 mg./kg. body weight, or mixed with the food. When given in the food it can be used over 2 days at 1 lb. per 100 lb. mash for each 200 adult birds or 300 growing birds. It can be combined with phenothiazine and nicotine sulphate for the treatment of mixed infestations. It had no deleterious effect on egg production of the birds.

Phenylmercuric phthalate

Guthrie & Harwood (1948) stated that 50 mg. phenylmercuric phthalate was highly effective against R. cesticillus. It had a therapeutic index of 10:1.

Halogenated aromatic compounds

Kerr (1948) tested hexachlorophene (2:2'-dihydroxy-3:3'-5:5'-6:6'-hexachlorophenylmethane) in fowls infested with R. cesticillus. A control test indicated 98 per cent efficiency. The therapeutic dose was 25-50 mg./kg. body weight but there was some depression of egg production of the birds for 7 days after treatment. The drug was compatible with phenothiazine and nicotine sulphate. Kerr & Green (1953) examined nine related compounds and only two of these, hexachlorophene and 2:2'-dihydroxy-3:3'-4:4'-5:5'-6:6'-octochlorodiphenylether, had high activity after a single oral dose. Dichlorophen yielded poor results.

Hymenolepis

There is very little experimental evidence on the value of drugs against Hymenolepis in birds. Russian workers have used arecoline in infested ducks and geese and also male fern in geese. It is likely that the reaction

of Hymenolepis is similar to that of Raillietina and some workers are of the opinion that R. cesticillus is one of the most difficult cestodes to remove from poultry. It would appear therefore that drugs which are effective against Raillietina can be recommended, with some reservation, against Hymenolepis. Guthrie & Harwood (1944) found that combinations of tin oleate with triethanolamine, ammonium hydroxide or pelletierine were effective, though they pointed out that such a treatment was of no practical value. The same authors in 1948 used 50 mg. phenyl mercuric phthalate which removed 70 per cent of the H. carioca harboured by the experimental birds.

Davainea

There is little information on experimental work with Davainea. Levine (1938) was unable to find any effective drug against Davainea. Guthrie & Harwood (1948) used 50 mg. phenyl mercuric phthalate but it removed only 50 per cent of the Davainea present. Little has been published on the effect of the newer poultry taeniacides against this species and a thorough trial of these compounds should be made.

Choanotaenia

Few specific tests have been made with Choanotaenia. Underwood, et al. (1938), found that brilliant green sulphate removed Choanotaenia from fowls but the drug was too toxic. The less soluble picrate was no more effective and proved to be almost as toxic.

EXPERIMENTAL ANIMALS

Male fern

The work of Holten (1947) has shown that male fern is effective against Hymenolepis diminuta in mice.

Acridines

Culbertson (1940) showed that mepacrine hydrochloride was effective in eliminating H. fraterna in mice. He used it in doses of 20 mg. per mouse, either given in two doses of 10 mg. on successive days, or 10 mg. followed by 5-mg. doses on alternate days, or 5-mg. doses on alternate days. The second schedule seemed to give the best results and was well tolerated. Smaller doses, 5 mg. on two successive days, did not eliminate the parasite but suppressed the egg production of the worms temporarily. Culbertson & Greenfield (1941) found that it retarded the development of Cysticercus fasciolaris but only when administration was commenced before infection.

Dyestuffs

Deschiens (1944) found that triamine dyes, basic fuchsin and methyl violet were more effective than the diamines, malachite green, methyl green, and brilliant green against Hymenolepis in mice.

Lagrange (1946) stated that alizarin will kill cysticerci in situ when administered to mice and that solutions of 1:10,000 prevented the evagination of the scolex.

Conessine chlorhydrate

Janot & Cavier (1949) reported that conessine had some effect in that it eliminated H. nana from 6 out of 10 mice.

DISCUSSION

From what has been mentioned above, it is clear that there is ample scope for improvements in the taeniacides generally. Further critical studies of those in common use might provide good grounds for discarding many of them. There are, however, several groups of compounds that have shown evidence of activity and which warrant further scrutiny. Duguid & Heathcote (1950b) have suggested that new anthelmintics might be sought among the simpler derivatives of piperidine or reduced pyridine. Rogers (1948) has pointed out that as the surface layers of the proglottid are rich in alkaline phosphatase, substances capable of blocking this enzyme might prove to be useful as taeniacides. There is scope for more work on organic tin compounds and on the acridine dyes, and comprehensive studies aimed primarily at relating structure or properties to anthelmintic action should be carried out.

There are two main lines of approach to new taeniacides. One is by random testing of large numbers of compounds. For this purpose a test organism is required that lends itself to routine evaluation on a large scale. Hymenolepis or Cysticercus in mice, Raillietina in chickens or the brood capsules of Echinococcus might all prove valuable for this purpose. When a substance shows evidence of activity it should be examined more closely for toxicity to the parasite and to the host. The next step involves the preparation and testing of large numbers of related compounds, the most promising ones being finally selected for further experiments with other host/parasite systems.

The alternative, which is undoubtedly the more rational approach to selective toxicity and one which, in other fields of chemotherapy, has given very spectacular results, is to seek analogues of parasite metabolites for use as anthelmintics. Unfortunately our present knowledge of cestode metabolism is very incomplete and consequently this method may fail to yield as rapid progress as random testing.

CONCLUSIONS

Of the drugs discussed above, only the following are considered to be suitable for clinical use, though others may qualify when further experimental data are forthcoming.

Man

extract of male fern, mepacrine hydrochloride, "tenamid";

Dog

arecoline hydrobromide, arecoline-acetarsol, dichlorophen, "anthelin";

Cat

arecoline-acetarsol, dichlorophen;

Sheep

lead arsenate, copper sulphate and nicotine sulphate;

Cattle

lead arsenate;

Poultry

di-n-butyl tin dilaurate, hexachlorophene.

APPENDIX

Trade Synonyms for Taeniacidal Drugs

Throughout the review, the names used for drugs are those used either in the British Veterinary Codex, the British Pharmacopoeia, the United States Pharmacopeia or the Extra Pharmacopoeia (Martindale). In only three instances have trade names been used ("anthelin", "stannoxyl", and "tenamid") and in these cases only for the sake of brevity. In the literature many authors use proprietary names and for that reason the following list of some of the more common ones is given.

Acetarsol = stovarsol, kharaphen, orarsen, spiricid vagival.
Aminacrine hydrochloride = acramidine, acramine, acramine yellow.
Arecoline-acetarsol = nemural, cestarsol, tenoban, drocarbil.
Di-n-butyl tin dilaurate = butynorate.
Chloraquin diphosphate = aralen diphosphate.
Chloraquin sulphate = nivaquin, nivaquin B.
Dichlorophen = dicestal, teniathane, diphenthane 70, compound G4.
Mepacrine hydrochloride = atabrine, atebrin, quinacrine, mecryl, metoquin.

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Toxoplasmosis in Animals

BY

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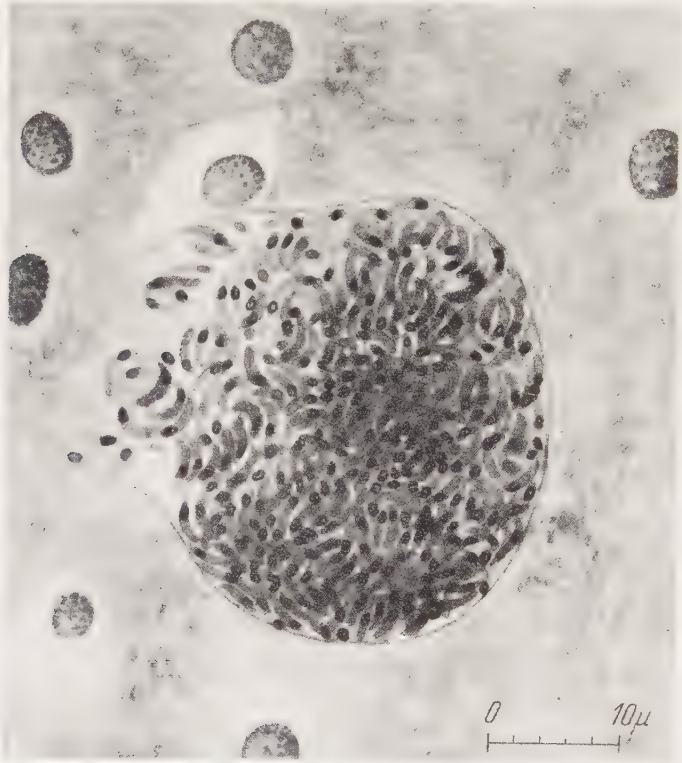
INTRODUCTION

Toxoplasma gondii has been known since 1908, when it was first described by Nicolle & Manceaux from a North African rodent, Ctenodactylus gundi. Since then toxoplasms were recorded from various wild and domestic animals in different countries. However, the interest in these parasites was purely zoological till 1939, when Wolf, Cowen & Page provided indisputable evidence of the occurrence of toxoplasmosis in man and Sabin established the morphological and immunological identity of human strains of the parasite with those from lower mammals. It then became evident that the causative organism of all forms of mammalian toxoplasmosis was represented by one and the same species, T. gondii. At first it was thought that human toxoplasmosis was a rare disease occurring only in certain localities but it soon became evident that it has a cosmopolitan distribution with a relatively high incidence. The absence of host-restriction in Toxoplasma, which is interchangeable between various animals and man, led to a search for possible sources of human infection among lower animals, with the result that a significant correlation was revealed between the incidence of toxoplasmosis in man and in some animals living in his immediate environment. Moreover, it has recently been shown that this disease is enzootic among livestock Toxoplasmosis is thus a typical zoonosis, which now claims a place in veterinary medicine, both because of the public health importance of lower animals as probable reservoirs of human infection and because of the prevalence of this disease among economically important mammals and birds. The importance of toxoplasmosis in human and veterinary medicine is reflected in the vast literature on the subject, which now lists about 2,000 titles (for bibliography see Eyles & Frenkel, 1952, 1954; and Lainson, 1955).

The nature of the causative organism, T. gondii, is so uncertain that — at the present state of our knowledge — it cannot be referred to any known group of Protista, but is provisionally attached to the Protozoa, among Sporozoa of doubtful position. Toxoplasma is typically an intracellular parasite which may attack almost any organ, with a predilection for elements of the reticulo-endothelial (or lymphoid-macrophage) and central nervous systems, but it also occurs free in various tissues. Its life-cycle is relatively simple: after invading the host-cell the parasite reproduces by repeated binary division, eventually giving rise to hundreds of daughter-individuals. In the course of multiplication this aggregation of parasites is invested in a tough protective membrane and is known as a

"pseudocyst", which soon becomes detached from the original host-cell and lies freely within or outside the tissue. It is thought that pseudocysts represent the propagative stage by which the infection is transmitted to new hosts, while the spread of the infection within the host's body is effected by the unencysted free parasites, possibly through the blood, in which they can be detected during certain periods of the infection. The type of tissues affected, the species of host and its age, as well as the strain of parasite, all determine the variable character of the symptoms and course of toxoplasmosis, the most important clinical manifestations of which are encephalitis, febrile exanthem with pneumonitis, and enterocolitis.



TOXOPLASMA GONDII. *Ruptured pseudocyst in brain of child.* (*From Piekarski*, 1950).

INCIDENCE

The host-range of Toxoplasma extends through most classes of vertebrate animals: thus spontaneous infections have been recorded from 45 species of mammals, 70 species of birds, and 5 species of cold-blooded animals. However, only the mammalian strains, and those avian strains which are infective to mammals, can be definitely attributed to T. gondii, whereas the identity of other avian strains, and especially of strains from cold-blooded vertebrates is uncertain. In view of these doubts, Garnham (1950) proposed the name Atoxoplasma for those toxoplasm-like parasites

of birds which are host-specific, while a number of workers have proved that cold-blooded vertebrates were refractory to infection with mammalian Toxoplasma (Coutelen et al., 1952; Kozar, 1952; Schmidt-Hoensdorf & Holz, 1952; Manwell et al., 1953). Among the mammalian and avian hosts of T. gondii there are a number, living in the human environment of different countries, which are actually or potentially of medical and veterinary importance. These animals are listed in the accompanying table.

Natural Hosts of Toxoplasma in the Human Environment

MAMMALS

Man: Homo sapiens
Pig: Sus scrofa
Cattle: Bos taurus
Sheep: Ovis aries
Dog: Canis familiaris
Silver Fox: Vulpes fulva
Cat: Felis ocreata catus
Raccoon: Procyon lotor
Ferret: Mustela (Putorius) furo
Rabbit: Oryctolagus cuniculus
Hares: Lepus europaeus, L. timidus
Squirrel: Sciurus vulgaris
Souslik: Citellus pygmaeus
Marmots: Marmota marmota, M. monax
Rats: Rattus rattus, R. norvegicus, R. turkestanicus
Mouse: Mus musculus
Voles: Microtus agrestis, M. sp.
Guinea-pig: Cavia porcellus
Chinchillas: Lagidium peruanum, L. viscaccia
Mole: Talpa sp.

BIRDS

Domestic Fowl: Gallus gallus
Pheasant: Phasianus colchicus
Capercaillie: Tetrao urogallus
Grouse: Lyrurus tetrix
Pigeon: Columba livia
Sparrow: Passer domesticus
Canary: Serinus canarius

The recorded incidence of toxoplasmic infection among animals associated in one way or another with man is only of relative significance, for the available figures do not necessarily reflect the true prevalence of the disease in a given country or host, but are the result of random sampling. Moreover, in those cases where the diagnosis was based solely on positive

serological reactions or clinical grounds, without confirmatory parasitological findings, the figures are unreliable, because (a) positive reactions to toxoplasmosis can be obtained with sera from patients suffering from other complaints, and (b) similar clinical symptoms may occur in diseases of non-toxoplasmic nature.

Toxoplasmosis is common in dogs. Thus among dogs examined in Switzerland Fankhauser (1952) found 6% infected, while surveys carried out by Otten, Westphal & Kajahn (1950, 1951) have shown that in Hamburg up to 5% of dogs were infected. In Britain only 2 - 3 cases of natural infection were known (MacIntyre et al., 1948; Bonser, 1950) until quite recently Campbell et al. (1955) described 16 more cases of canine toxoplasmosis from Scotland, which were detected post-mortem among 268 dogs suffering from distemper, while Lainson (1955) demonstrated that in London some 40% of the dogs examined serologically reacted positively. On the other hand, in the U. S. A., Cole et al. (1953, 1954) have described epizootic outbreaks with high mortality from several kennels. The spontaneous occurrence of toxoplasmosis has also been recently recorded in the United States from widely separated herds of cattle (Sanger et al., 1953), and outbreaks of this disease have been described from pigs and sheep (Cole et al., 1953, 1954). A number of cases have also been reported from cats (Olafson & Monlux, 1942; Holzworth, 1954), while serological tests revealed the infection in 34% of these animals in the U. S. A. (Miller & Feldman, 1953). Isolated cases of toxoplasmosis in fowls have been recorded on several occasions, but Erichsen & Harboe (1953) were the first to describe a fatal epizootic outbreak in a flock from Norway, and Nobrega et al. (1954) reported an outbreak, with 50% mortality, among fowls in Brazil. Among the smaller domestic animals toxoplasmosis is frequently encountered in rabbits. Thus spontaneous cases — including epizootics — were reported by Wiktor (1950) and Morel (1954), while Lainson (1955) demonstrated the presence of toxoplasms in 6% of domestic rabbits examined in Britain and Beverley et al. (1954) obtained positive serological reactions in up to 34% of these animals examined in Great Britain.

Outbreaks of toxoplasmosis have also been observed among laboratory rodents (Mooser, 1950; Vivell & Buhn, 1952). Pigeons are particularly susceptible to this disease: thus Jacobs et al. (1952) found 12% infected in Washington, and the disease in these birds is enzootic in Uruguay (Cassamagnaghi, 1952), while in a number of instances epizootics have also been reported (Johnson, 1944; Wiktor, 1950). Among wild hosts in the human environment, toxoplasmosis occurs in some game and fur-bearing animals, as well as in household and field pests. Thus in Czechoslovakia up to 10% of hares were found to be affected with this disease (Jirovec, 1952), which in Scandinavian countries produced a number of epizootics (Hülphers et al., 1947; Christiansen & Siim, 1951; Borg, 1953). Outbreaks have also been described among capercaillies (Borg, 1953) and chinchillas (Keagy, 1949), and spontaneous infections occur in rats (Perrin et al., 1943; Laven & Westphal, 1950; Lainson, 1955) and voles (Findlay & Middleton, 1934; Laven & Westphal, 1950).

CLINICAL AND PATHOLOGICAL ASPECTS

The clinical course of toxoplasmosis has been studied more fully in man, in whom the type of disease varies, according to whether the infection was contracted in utero (congenital) or after birth (acquired or postnatal). Congenital infections of infants are characterized chiefly by disorders of the central nervous system, with symptoms of necrotizing encephalomyelitis, chorioretinitis, cerebral calcifications and neurological disturbances. Acquired infection in older children is manifested mainly by encephalitis, whereas in adults it is an acute febrile exanthem with pneumonitis, but without cerebral involvement. However, the majority of adult cases are symptomless carriers, in whom the latent infection is revealed only by positive serological reactions or — in the case of mothers — by congenital infection in their offspring. The pathological changes in the tissues take the form of multiple proliferative granulomata with signs of necrosis, which are thought to be due to elaboration by Toxoplasma of a powerful exotoxin.

In general, the clinical course and pathology of toxoplasmosis in animals follow the human pattern, as shown in the following brief account of the disease in the more important domestic animals.

Dogs

In a recent experimental study of canine toxoplasmosis Jacobs et al. (1955) have shown that, whereas young animals develop an acute disease of short duration (3 months), in adults the infection runs a symptomless or subclinical course. According to Fankhauser (1952), there are two types of the disease in dogs: (a) the visceral form, characterized by fever, loss of condition, gastro-enteritis with diarrhoea, and pneumonitis, with death ensuing in 2 - 10 weeks, and (b) the nervous form, manifested by psychic disturbances and locomotor disorders, while some of the clinical symptoms resemble distemper and "hard pad" disease. However Campbell et al. (1955) have shown that in some cases canine distemper may be associated with toxoplasmic infection which is masked by symptoms of the former disease. In the brain lesions of meningoencephalitis are present, but there is no calcification. In the intestine the parasites invade the wall, producing ulceration of the mucosa, whence they escape into the lumen and may be discharged with the faeces, in which parasites have been detected (Cole, Prior, Docton, Chamberlain & Saslaw, 1953; Jacobs et al., 1955). There is also evidence that toxoplasmosis in dogs may be acquired congenitally (Chamberlain et al., 1953; Cole et al., 1953, 1954).

Cats

The disease in cats is similar to that in dogs (Olafson & Monlux, 1942; Holzworth, 1954).

Cattle

In cattle the infection may run an acute course, with symptoms of fever, dyspnoea and extreme weakness, as well as of central nervous disorders. The disease is fatal in some cases, while in others the animals may recover. The pathological changes include necrotic foci and calcifi-

cations in brain tissue, with parasites in the cerebral lesions, in the lungs and bronchi, as well as in the spleen. Furthermore, the finding of toxoplasms in the uterus of cows and in the organs of new-born calves provides evidence of congenital infection (Sanger et al., 1953).

Pigs

Toxoplasmosis in pigs is of the same type as in cattle. In an epizootic outbreak with 50% mortality, observed in the U. S. A. (Cole et al., 1953, 1954), the disease was manifested by symptoms of debility, incoordination and enteritis with diarrhoea, but fever was absent. Some of the pathological changes were characteristic of pneumonia, and necrotic foci were present in the liver and brain, with parasites in the affected organs. The presence of toxoplasms in stillborn and new-born piglets pointed to congenital infection.

Sheep

According to Cole et al. (1954), ovine toxoplasmosis is characterized chiefly by symptoms referable to the respiratory and central nervous systems, with necrotic and granulomatous lesions in the corresponding organs. Infected ewes sometimes aborted or gave birth to diseased lambs, in which the congenital nature of the infection was confirmed by the finding of pseudocysts in the placenta and uterine wall of the ewes.

Fowls

In an epizootic outbreak among fowls, described by Erichsen & Harboe (1953), the identity of the parasite with T. gondii was confirmed by its transmission to mice and by serological tests. The most constant lesions seen in the birds were those of peri- and myocarditis, encephalitis and ulcerating gastro-enteritis.

In addition to overt toxoplasmosis recorded from domestic animals, American workers have demonstrated that a large proportion of the animals gave positive serological reactions, viz. 34-59% in dogs, 34% in cats, 47% in cattle, 30% in pigs, and 48% in goats. These findings indicated "that much undiagnosed clinical toxoplasmosis or considerable benign disease exists in animals of veterinary medical importance" (Cole et al., 1954). In fact, there is considerable evidence that in the majority of cases of toxoplasmosis the infection runs a symptomless latent course, and the host-parasite relations are typically harmonious, whereas acute disease and epizootic outbreaks — though more conspicuous — are the exception.

TRANSMISSION

Very little is known about the mode of transmission of toxoplasmosis in nature, while attempts to solve this problem experimentally have produced inconclusive results. The only method of transmission established beyond all doubt, in man and in lower animals, is the congenital one. Intrauterine infection of the offspring has been demonstrated both experimentally (Kåss, 1952; Hellbrügge, Dahme & Hellbrügge, 1953; Wildführ, 1954)

and under natural conditions (Cole et al., 1953, 1954; Sanger et al., 1953). With regard to the mechanism of congenital transmission, it is probable that the parasites first invade the placenta, and then infect the foetus, a view which is supported by the finding of toxoplasms in the uterine wall of mothers and in the placenta.

The occurrence of parasitaemia in infected animals has suggested that blood-sucking arthropods might serve as vectors. However, practically all attempts to produce infection through the bites of insects and ticks, which had previously fed on infected animals, have failed, though their teased-up tissues were sometimes infective to rodents (Piekarski, 1949; Laven & Westphal, 1950; Blanc, Bruneau & Chabaud, 1951; Weyer, 1951; Jacobs, 1953; Woke et al., 1953). Nevertheless, the possibility of purely mechanical transmission through biting arthropods cannot be excluded.

There is growing evidence of transmission by the oral route, which has been produced experimentally by feeding animals with infected tissues (Kozar et al., 1952; Lainson, 1954; Weinman & Chandler, 1954). Moreover, it has recently been shown (Lainson, 1955) that in carcasses and brains of infected rodents the toxoplasms remain viable and infective for several days after storage at room temperature and in a refrigerator. These findings suggest that dogs and cats — as well as other carnivores — might become infected by eating small mammals (e.g. rabbits). Similarly, the meat or viscera of infected food animals might be the source of human infection, especially in view of the fact that Sanger et al. (1953) have demonstrated the presence of toxoplasms in beef carcasses. It is also conceivable that the infection can be transmitted from mother to offspring through the milk, in which toxoplasms have been detected in the case of murine species, bitches, sows and cows (Eichenwald, 1948; Laven & Westphal, 1950; Cole et al., 1953, 1954; Chamberlain et al., 1953). There are also indications that toxoplasmosis might be transmitted by contamination with the faeces or urine of infected animals, in cases where the intestinal wall is parasitized (Olafson & Monlux, 1942; Adams et al., 1949; Laven & Westphal, 1950; Westphal, 1951), though this possibility is minimized or denied by some authors (Kozar et al., 1952; Schmidtke, 1954, a, b; Jacobs et al., 1955; Lainson, 1955).

The occurrence, in some animals affected with toxoplasmosis, of pulmonary symptoms and rhinitis has raised the question of droplet transmission. In such animals free pseudocysts have been found in the lumina of the alveoli and bronchioles, whence they are presumably discharged with the sputum (cf. Lainson, 1955), while Kåss (1952) proved that the nasal secretion of infected rabbits was infective to other animals. It is conceivable that in herbivorous animals the infection is acquired from grass contaminated with saliva or nasal discharge of infected animals. The possibility of droplet transmission finds experimental support in the successful infection of rodents after exposure to sprays of vaporized suspensions of toxoplasms (Kunert & Schmidtke, 1954).

Since chronic and latent infections are the predominant forms of toxo-

plasmosis, and they are associated with the presence of pseudocysts, persisting in the tissues for years, it is reasonable to assume that asymptomatic carriers are the main hosts responsible for the propagation of the disease, which is transmitted by means of the pseudocysts.

RESERVOIRS OF HUMAN INFECTION

Owing to the absence of host-restriction, toxoplasmic infection is interchangeable between a wide range of animals, including man. Theoretically, therefore, it is conceivable that any infected animal might be a source of human infection. It is obvious, however, that the risk of infection is greatest from animals in the human environment, and especially those with which man comes in close contact, some of which can be regarded as potential reservoirs of human toxoplasmosis. Although no single animal species has so far been actually incriminated in the transmission of the disease to man, there is considerable circumstantial evidence that rabbits, dogs, farm animals, birds, and perhaps some game animals, might act as reservoirs. Thus Beverley et al. (1954) have demonstrated that in Sheffield the proportion of human cases with positive serological reactions was significantly higher among persons handling rabbits or their carcasses professionally (e. g. veterinarians, abattoir workers, trappers) than in the general population. These findings are correlated with a high incidence of rabbit toxoplasmosis in Great Britain, established serologically by these workers and parasitologically by Lainson (1955). A number of observers have also demonstrated a definite correlation between human and canine infections in the same household (Westphal & Finke, 1950; Cole, Prior, Docton, Chamberlain & Saslaw, 1953), and it has also been shown that toxoplasmosis is practically an occupational disease among persons handling dogs professionally (Otten & Westphal, 1951). It is not clear, however, whether man acquires the infection directly from dogs, or both become infected from a common source (Jacobs et al., 1955; Lainson, 1955). Since toxoplasms may be present in the muscles of infected cattle and pigs, it is also conceivable that man may be exposed to infection by handling their carcasses or by consuming undercooked beef or pork (Sanger et al., 1954; Weinman & Chandler, 1954). Among birds, suspicion has fallen on pigeons, a high proportion of which are naturally infected in the U. S. A. (Manwell & Drobeck, 1951; Jacobs et al., 1952). With regard to wild animals, it may be significant that, in his observations on outbreaks among hares and capercaillies in Sweden, Borg (1953) found that the geographical distribution of human and game toxoplasmosis coincided.

TREATMENT

The search for effective treatment of toxoplasmosis has been going on for many years, in the course of which trials were carried out with a great variety of chemotherapeutic and antibiotic agents. Though some promising results were obtained with a few drugs, none of them proved to be entirely satisfactory until American workers (cf. Eyles & Coleman, 1955) demonstrated the therapeutic effect of daraprim (pyrimethamine) and sulphadiazine in the treatment of experimental toxoplasmosis in mice. It

was found however that, when used separately, neither of these drugs cured more than 50% of the animals, but when the two were administered jointly, they had a strong synergistic action, producing a maximum curative effect in up to 100% of the cases treated.

The efficiency of this treatment was recently confirmed in clinical cases by Czechoslovakian workers (Petrovicky, 1955; Petrovicky & Styblova, 1955), who successfully cured a number of cases of human toxoplasmosis with daraprim, used alone or combined with the sulphonamide.

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Magnesium Metabolism in Cattle

BY

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This paper is concerned with the requirements of cattle for magnesium and the aspects of magnesium metabolism which appear to be of importance in accounting for the incidence of the diseases which are classified as hypomagnesaemic tetanies. No attempt has been made to review the whole of the vast literature on the subject of hypomagnesaemia since many excellent accounts have already appeared such as that by Allcroft (1954) in which an account of the earlier investigations is presented. Some of the work referred to has not been published.

INCIDENCE OF THE HYPOMAGNESAEMIC DISEASES

When first noted and recognized in Britain in the 1930's, tetany in cattle appeared rather limited in its geographical distribution. The very name "Hereford disease" emphasizes that it appeared to be a local problem. Now these diseases are much more widely dispersed and this has been emphasized by many. White (1952), for instance, has drawn attention to its changed incidence and location in his practice over a period of 20 years. Such changes appear to be real rather than due to failure to recognize the condition in earlier years, but the absence of vital statistics for farm animals makes quantitative assessment impossible. One must be content with the wealth of practical opinion which states that incidence and geographical distribution of the disease have increased and that these increases are closely linked with improvement of crop, pasture and animal husbandry (see, for instance, King, 1954).

Recent surveys by Withers (1955) in the south of England indicate that 3 to 10% of dairy herds experience trouble with the disease and that its annual incidence is between 1 and 5 cases per 1,000 cows. A Scottish survey of veterinary practice provides a similar figure of 1 to 2 cases per 1,000 animals at risk (Grunsell & Paver, 1955). Dutch workers (Seekles & Boogaerdt, 1955) place the incidence at 10 to 20 per 1,000 animals. Calf tetany in beef herds in North Scotland has been found to have a 5 to 7% incidence on a herd basis and a low annual death rate, (Blaxter & Sharman, 1955). The incidence is thus low, much lower for instance, than that of acetonaemia or milk fever. The disease is of economic importance because the death rate is very high, and often the only indication of its presence is a sudden and unexpected death.

The disease has a seasonal incidence, a maximum occurring in the spring when the animals are turned out to pasture and a usually less-pronounced peak in the winter (Allcroft, 1947a). The early descriptions of

the disease, in fact, emphasized unduly its high incidence when cattle are turned out to grass in the spring (Sjollema & Seekles, 1929; Dryerre, 1932; Blakemore & Stewart, 1933-34), and it was not until 1938 when Allcroft & Green recorded seasonal hypomagnesaemia in cattle in the winter months, that the disease was regarded as other than a metabolic disturbance associated with the first flush of spring grass. The seasonal hypomagnesaemia of cattle with low serum concentrations occurring in winter has been well confirmed (Allcroft, 1947b; Barker, 1948; Inglis et al., 1954).

TABLE 1

The age incidence of hypomagnesaemic tetany in cows, the age structure of the cow population and the relative susceptibility of cows to the disease (heifer lactation = unity)

Age calculated in lactations	Incidence of hypomagnesaemia % of total calved cows	Age distribution of cows in herds (%)		Relative susceptibility to tetany (1st lactation = 1)
		Pettit 1947	M. M. B. 1947	
1	4.1	23.5	25.6	1.0
2	8.9	22.5	21.6	2.3
3	20.9	20.6	16.9	5.9
4	23.6	13.0	13.8	10.6
5	14.0	8.2	9.2	10.1
6	13.4	5.2	5.7	15.2
more than 6	15.1	6.3	7.2	14.0
Total	100.0	100.0	100.0	—

Within any one herd affected by the disease the incidence of the clinical condition is restricted to a limited number of individuals. Analyses of the serum of clinically unaffected animals may indicate in some instances a general reduction in Mg concentration. At other times, the majority of the cows may have blood serum concentrations of Mg within the accepted normal range. The many "herd studies" of serum concentrations of Mg following or during "outbreaks" make this abundantly clear, and Green's (1948) postulate that the disease can be broadly classified into rapidly developing and slow (seasonal) developing types clearly takes cognizance of this. In calves, the disease is of the "slow" type, and usually the whole of the stock is affected. It is, in fact, important to note that the slow type of the disease and generalized seasonal hypomagnesaemias are often limited to young or growing stock. In cows the onset of the condition is in the majority of instances rapid, and usually, but not invariably, coincides with the first flush of grass in the spring.

In Allcroft's statistical study of hypomagnesaemia, an attempt was made to find, in the instance of the adult disease, which cows were the

most susceptible (1947a). No breed differences were apparent, beef cows and dairy cows both being affected. The age distribution of cases gave a maximal number at the third to fourth calvings, and Allcroft commented on "the association of hypomagnesaemia with the earlier calvings". This large number of cases of hypomagnesaemia occurring in the earlier lactations, however, needs consideration in relation to the age structure of the population as a whole before it can be properly interpreted. Table 1 shows the percentage incidence of hypomagnesaemic tetany calculated from Allcroft's data, together with two estimates of the age structure of the cow population of the country (Pettit, 1940; Milk Marketing Board, 1947).

The final column of Table 1, calculated from the incidence and age distribution figures, shows the relative susceptibility of animals of different ages. Old cows, which have had more than 6 calves, are 14 times more likely to develop the disease than are heifers in their first lactation. Such statistics are in agreement with earlier observations in Holland by Sjollema (1932). The effect of age raises a further point, namely to what extent the present apparent increase in the incidence of tetany might arise from changes in the age structure of the cattle population following on control of tuberculosis, mastitis, contagious abortion and other epidemic diseases*.

Finally, in assessing individual susceptibility, it appears from Allcroft's data that there is no close association of the incidence of hypomagnesaemia with the lapse of time since parturition - unlike milk fever (hypocalcaemia), where incidence is highest immediately after calving.

NUTRITIONAL ASPECTS

In accounting for the incidence of hypomagnesaemic diseases workers appear to have adopted two points of view which though apparently diametrically opposed are now tending to merge. On the one hand the disease was regarded as a metabolic disorder, a physiological dysfunction in which neural and endocrine factors and environmental stresses are paramount and in which the nutritional status of the animal is of little or no account (Green, 1948, 1950). On the other hand, the disease was regarded as of complex dietetic origin. The relation between the incidence of the disease and the presence in the pasture of apparent excesses of dietary essentials such as protein (Sjollema & Seekles, 1933) or potassium (Seekles & Sjollema, 1932), and the fact that following oral administration of Mg the incidence of the overt syndrome ceased (Blakemore & Stewart, 1934-5; Allcroft, 1947b; Allcroft, 1953; Stewart, 1954), certainly suggest that the supply of magnesium and other dietary factors and the availability to the

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Footnote

* It may also be pointed out that a similar recalculation of Allcroft's statistics on the incidence of hypocalcaemia shows an even greater susceptibility of the old cow relative to the heifer than occurs with hypomagnesaemia.

animal of the Mg of natural feeds cannot be ignored. However, those who would seek an orthodox nutritional explanation cannot afford to ignore the fact that the serum Mg concentration can fall precipitously within a matter of two days when the ration of an adult animal is changed (Stewart, 1954; Allcroft, 1954). Such effects can hardly be due to a dietary deficiency of Mg in the classical sense, especially since the animal "recovers its equilibrium" even when it is kept on the ration which induced the effect. The physiological mechanisms which operate to maintain the extracellular concentrations of the Mg ion must thus be considered as well, since it appears that depletion of the Mg ion concentration in the fluid bathing neuromuscular junctions and synapses is responsible for the tetanic syndrome (Blaxter et al., 1954).

MAGNESIUM REQUIREMENTS

As a starting point it is necessary to consider the requirements of cattle for magnesium. The net quantity of Mg which an animal requires each day is determined by the amount deposited in its tissues during growth, the amount secreted in the milk of lactating animals, and the amount needed to meet maintenance requirements, i.e. to compensate for those inevitable losses in the urine and faeces which occur even when the animal receives no dietary Mg. The actual dietary requirements involve considerations of the availability of Mg in dietary sources, while the techniques of the metabolic trial can be used to assess the adequacy of diets.

The body of the calf at birth contains about 20 g. Mg, some relevant data on whole carcasses being given in Table 2.

TABLE 2

The calcium and magnesium content of the whole bodies of calves at birth (Haigh, Moulton & Trowbridge, 1920)

Weight of calf (kg.)	Calcium content (g.)	Magnesium content (g.)
40.4	705	24.6
33.5	544	20.1
24.0	304	12.3
13.6	173	6.3

The relation of the Mg content of the body to body weight is given by the equation:

$$\text{Mg (g.)} = 0.655 \text{ Weight (kg.)} - 3.5$$

The Mg content of the new tissues formed by the growing animal is approximately 0.6 g./kg., varying fairly widely according to the relative

degree of skeletal and soft tissue growth. Thus the fresh skeleton contains about 1.5 g. Mg/kg. and the soft tissues only about 0.2 g. Mg/kg., so that the Mg content of 1 kg. of live weight gain in an animal growing rapidly in skeletal size is considerably greater than that in one depositing muscle and fat.

In Tables 3 and 4, an attempt has been made to calculate minimal dietary requirements of Mg. Skeletal growth was assessed from the normal rate of accumulation of body calcium while soft tissue growth was assessed from the normal rate of accumulation of N. Maintenance requirements for Mg were based on the losses of Mg from the body in calves given diets low in the element, as 3–4 mg./kg., and the lower figure has been taken (Blaxter & Rook, 1954). Our own metabolic studies with cows (unpublished) indicate that adults lose about 1.5–2.0 g. Mg (3–5 mg. Mg/kg.) under similar conditions, suggesting that the estimate from work with calves is a reasonable one. The Mg content of milk is based on analyses of the milk of normal cows receiving adequate Mg.

The availability of dietary Mg for cattle is low compared with that of dietary Ca. Experiments with calves (Blaxter & Wood, 1952) have shown that in the growing calf the availability of dietary Ca approaches 95%. This high efficiency falls with age to about 70% in the adult. Similar experiments with Mg indicate that the calf does not retain the element very efficiently. Estimates of availability obtained from balance trials (Blaxter & Rook, 1954) showed that only 30–50% of the dietary Mg was available to meet body demands. It seems reasonable to take as an estimate of the average availability of dietary Mg a figure of 33%, realizing that this may well be too high an estimate under some conditions and in older animals. It may be pointed out that the low availability arises from a large faecal loss of the element. A large part of this represents an inevitable loss of the element through unabsorbed digestive juices and occurs even when no Mg is given at all. The experiments of Garner (1950) indicating that from 20–60% of dietary Mg was excreted in faeces cannot be used to provide estimates of availability since urine losses of Mg were not measured.

Using 33% as the availability of dietary Mg, the minimal requirements given in the last column in Tables 3 and 4 are obtained. The figures show that lactation greatly increases Mg demands. In the instance of the lactating dairy cow yielding 4 gal. of milk and consuming 28 lb. dry weight of grass, the dietary need of 12.8 g. is met by a dietary concentration of Mg of 0.1% of the dry matter. It is important to realize that the estimates above are estimates of minimal requirements and include no margins of safety.

Their reliability can, however, be checked from the metabolic balances — admittedly limited in number — which have been made with cattle. Experiments with lactating cows yielding 20–30 lb. of milk (Blaxter, Presthegge & Wood, unpublished) showed that small positive retentions of Mg were achieved at dietary intakes of 10.6 g., 12.9 g., 17.4 g., 17.5 g., and 22.9 g. of Mg daily. When the intake of Mg was reduced to 4.9 g. and

TABLE 3

Calculated minimal requirements of dietary magnesium by rapidly growing dairy heifers

Weight of animal (lb.)	Age (months)	Daily gain (lb. /day)	Daily increments of					Maintenance requirement of magnesium (4) (g.)	Net requirement /day (g.)	Actual requirement /day (5) (g.)
			Calcium (1) (g.)	Nitrogen (1) (g.)	Magnesium					
					in skeleton (2) (g.)	in soft tissues (3) (g.)	Total (g.)			
150	2.2	2.0	12.3	32.3	0.27	0.23	0.50	0.20	0.70	2.10
200	3.0	2.0	11.9	30.6	0.26	0.22	0.48	0.27	0.75	2.25
400	6.6	1.8	10.4	24.6	0.23	0.18	0.41	0.53	0.94	2.82
600	10.6	1.5	9.1	18.9	0.20	0.13	0.33	0.80	1.13	3.39
800	15.4	1.3	7.7	13.8	0.17	0.10	0.27	1.07	1.34	4.02
1,000	21.3	1.0	6.3	9.1	0.14	0.06	0.20	1.34	1.54	4.62
1,200	28.9	0.7	6.9	4.8	0.15	0.04	0.19	1.61	1.80	6.40

(1) Taken from the calculations of Mitchell & McClure (1937) and Mitchell (1947).
(2) Calculated from a Ca : Mg ratio of normal bone of 45 : 1 (Blaxter & Rook, 1954).
(3) Calculated from the N : Mg ratio of muscle and soft tissues of 140 : 1 (Blaxter & Rook, 1954).
(4) Calculated from balance experiments on Mg free diets as 3 mg./kg. body weight (Blaxter & Sharman, 1955).
(5) Assuming that the availability of dietary Mg is 33%. See text for discussion.

TABLE 4

Calculated minimal Mg requirements of lactating cows

Milk yield (lb.)	Requirement of Mg[1] (g./day)	
	Net	Actual[2]
10	2.41	7.23
20	3.02	9.06
30	3.64	10.92
40	4.25	12.75
50	4.86	14.58

(1) Milk Mg was taken to be 13.5 mg./100 ml.
(2) Assuming dietary Mg to be 33% available.

6.5 g./day there was a loss from the body of 1.3 and 0.9 g. Mg. respectively. These results indicate that the minimal requirement is, in fact, of the order of 9–11 g. as the table suggests. Confirmatory evidence comes from long-term experiments made by Ender et al. (1949) who showed that hypomagnesaemic tetany could not be produced in lactating cows when an intake of 9–11 g. Mg was provided daily. With heifers, the observations of Parr & Allcroft (1953) showed that no significant hypomagnesaemia could be produced in 2-year-old beasts by giving them 4.7 g. Mg daily. This amount is about the minimum estimated requirement of Table 3. Again, the experiments in the north of Scotland with calves in which a similar calculation was made, showed that the low dietary intake of Mg was responsible for the incidence of the disease (Blaxter & Sharman, 1955). The large series of balance experiments with lactating cows, made by Forbes and his associates (1916, 1917, 1918), in which intakes of Mg were usually above 20 g. daily, revealed a number of negative balances of Mg, particularly in early lactation when the cows were also losing body Ca. Over longer periods — 200 days — however, the cows were always in positive balance as might be expected from the tables. The significance of Ca-Mg relationships is dealt with later. The long-term experiments by Groenewald in South Africa (1935) were carried out using dietary intakes of Mg of approximately 7–8 g. Average milk yields were 15 lb. daily. No fall in the serum Mg occurred, there was no tetany and the cows remained healthy. These results would also suggest that the estimates of requirement are adequate since a cow yielding 15 lb. of milk would, according to our calculations, requ re approximately 8 g. Mg daily.

There is, however, evidence from Indian balance experiments that

for some types of ration, the estimates of Tables 3 and 4 are not sufficient. Careful work by Ray (1942) in which wheat straw containing 0.15% Mg was given to heifers weighing approximately 400 lb. showed that the ration induced losses of body Mg and hypomagnesaemic tetany, whereas when hay containing 0.42% Mg was given there was a normal retention of the element

TABLE 5

The relation between dietary intake of Mg and serum Mg concentration in the experiments of Breirem et al. (1954)

Experiment	Ration	Mg intake /day (g.)	Mean serum concentration of Mg (mg./100 ml.)	Interpretation of serum magnesium concentration
I	A (cellulose and herring meal)	10.3	1.62	low
	B (cellulose and concentrates)	21.5	2.33	normal
	C (home-grown foods)	27.4	2.58	normal
II	A (cellulose and herring meal)	9.0	1.07	very low
	C (energy deficient diet, 20% below normal including straw)	11.4 to 16.4	1.65	low
	+ D B (home-grown foods)	24.3	2.35	normal

and the animals were healthy. From this work Ray concluded that the Mg requirement was approximately 14 mg. Mg/lb. body weight, or 5.6 g. for a 500 lb. animal, a value nearly 50% higher than our own estimates. Similarly, Carberry et al. (1937) found that the Mg of different foods was not equally available to cattle, and that the Mg content of the ration was not a reliable guide as to whether it would maintain an adequate retention of the element. The above authors, working with oxen, found in several instances that intakes below 7.0 g. Mg were associated with losses of the element from the body though intakes above 9.0 g. were invariably associated with its retention. These estimates of requirement are again almost 50% higher than our estimates of minimal requirement. They apply to beasts given rice straw, the significant point being that when certain

samples of straw were fed, losses of Mg occurred although their Mg content was higher than that of other samples which were associated with retention of Mg. This is not unexpected. Working with rats, Kunkel & Pearson (1948) found the availability of the Mg of magnesium oxide to be only 61% of that of the sulphate, and the availability of the Mg of the wheat plant to be only 76% of that of the sulphate. Further evidence that the estimates of minimal requirement may not be entirely adequate is to be found in the experiments of Breirem et al. (1954). In these the daily intake of Mg can be compared with the average serum concentration of Mg as in Table 5.

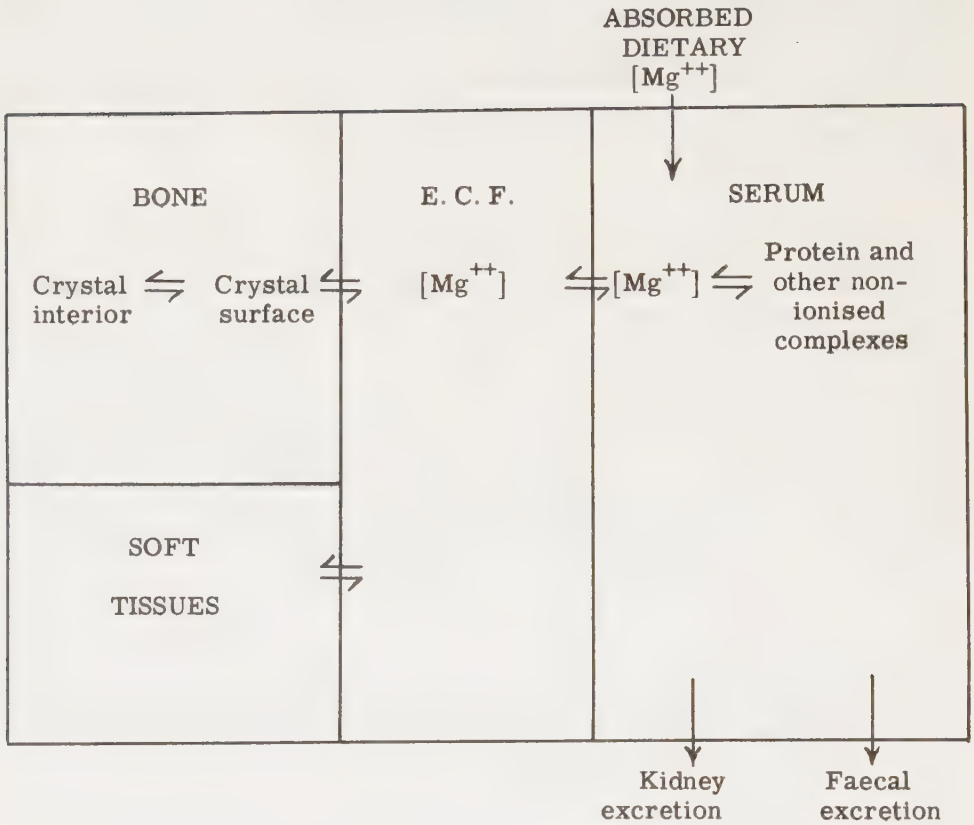
It will be noted that two of the groups of cows fed rations at about the minimal requirement of 9–11 g. failed to maintain normal serum Mg concentrations and that one group fed a ration containing straw and deficient in energy could not maintain normal serum concentrations although the cows received 11–16 g. Mg daily. It may be pointed out that these results of Breirem et al. do not agree with those of Groenewald (1935), previously cited. Nevertheless, their internal agreement, together with the results of the Indian experiments, suggest that the estimates of minimal requirement given in Tables 3 and 4 are not sufficient to cover all eventualities. Perhaps the estimate of 33% availability of dietary Mg may be too high: with some foods the availability of dietary Mg may be as low as 20%, i.e., the requirements are, in fact, 50% higher than those given in Tables 3 and 4.

The above balance experiments and calculations of the minimal requirements of Mg apply to animals which are in equilibrium with their rations. They provide no information on the adjustments which take place within the animal in order to maintain or attempt to maintain the concentration of Mg in the serum when the ration is changed to give a larger or smaller intake of Mg. Information on these aspects of Mg metabolism can be obtained from the results of experiments in which nutritional deficiencies of magnesium have been produced.

THE INTERNAL ECONOMY OF MAGNESIUM

In experiments with rats given rations almost devoid of Mg (Watchorn & McCance, 1937; Duckworth et al., 1940) the bone tissue was the major source from which Mg was lost to the body, little if any being lost from soft tissues. This has been confirmed in experiments with calves and, furthermore, it has been demonstrated that in this species there is a massive translocation of the element from the bones to the soft tissues during growth on Mg deficient rations (Blaxter & Rook, 1954; Blaxter, 1956). The extent of the transfer depends on the rate of soft tissue growth, since the Mg content of muscle, brain and other soft tissues remains virtually constant even though the extracellular concentration of the element has fallen very considerably. The bones thus serve as a labile reserve for Mg, providing, in the absence of a dietary source, Mg for soft tissue growth and for the inevitable excretion of the element in the urine and faeces.

FIGURE ONE

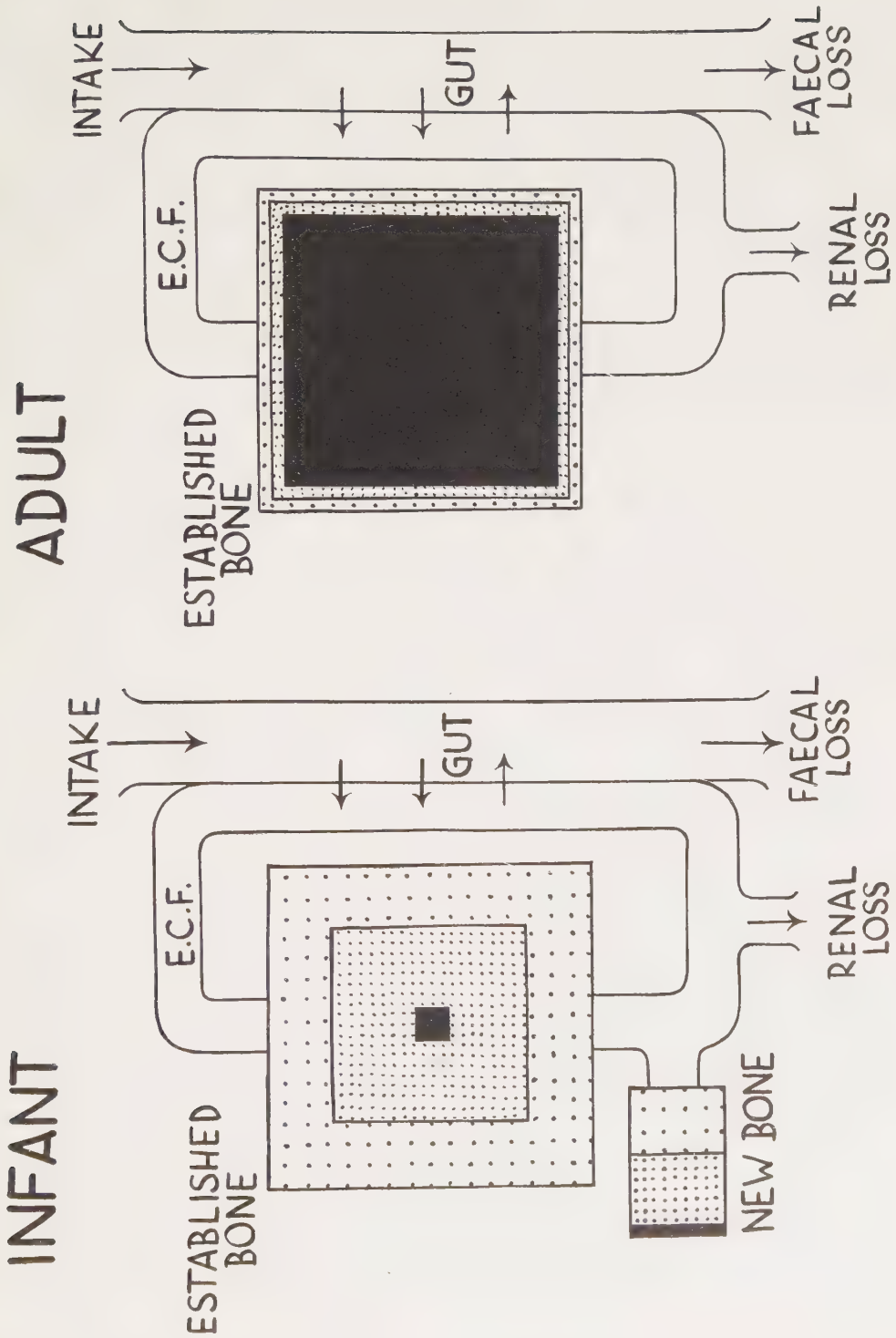


CAPTIONS TO FIGURES

Figure I Diagrammatic representation of Mg-homoeostasis in the animal body.

Figure II The general relationships governing the metabolic availability of the Mg of the skeleton of infant and adult animals. The outer layer of the established bone represents the exchangeable Mg present at crystal surfaces, the second layer Mg present in the recrystallizing portion of bone and the centre area, the Mg in the inert established osteons of the compact bone. The sharp lines of demarcation of the areas are diagrammatic. In fact, there is an infinite series of rates of fluid exchange, ionic exchange and recrystallization from very fast in areas of new calcification to very slow in established Haversian systems in adult compact bone.

FIGURE TWO



(ADAPTED FROM NEUMAN & NEUMAN, 1953)

The evidence from bone analyses in young calves shows that whenever a Mg ion is removed from the bone, it is replaced by a Ca ion (Blaxter, 1956). In other words, Mg can be lost from bone without concomitant loss of Ca, in fact, more usually the Ca content of the bone increases. This phenomenon can be explained in terms of a simple exchange between the extracellular fluid bathing the bone crystal surface and the surface ions of the bone crystal. Recrystallization of the bone mineral takes place as well, but this is a much slower phenomenon. The bone crystal surface acts, in fact, as a reservoir of Mg to be drawn upon in the face of increased demands from the tissues as in rapid growth or augmented lactation or increased secretion of the element into the digestive tract. It can also be drawn upon in the face of sudden changes in the Mg intake of the animal. The relationships are shown diagrammatically in Figure I.

Conversely, uptake of Mg by the bone will depend on the maintenance of a high concentration of Mg ions relative to Ca and Na ions in extracellular fluid at the crystal surface. In this connexion, it has been found in calves that when the serum Ca concentration is maintained at high levels for long periods, the Mg concentration in the serum falls despite an adequate dietary supply of the element (Blaxter, Hutcheson & Blackburn, unpublished). Little is yet known, however, of the time relationships of these surface exchanges, except indirectly. The deficiency experiments with calves indicate that it may take 40–50 days to deplete the skeletal Mg reserve, but that to build up the reserve once more may take a much longer period (Blaxter & Rook, 1954). In the Mg deficient rat, reparation of the deficiency of the bones has also been shown to be a slower process than their depletion (Duckworth & Godden, 1943).

Radioactive tracer studies of exchange processes in bone, using laboratory animals, show that in adults there is considerably less bone surface available for these exchange reactions (Bonner, 1948; Copp et al., 1951; Hansard et al., 1951) than there is in the infant animal. This is illustrated in Figure II, which is a modification of a diagram in the paper of Neuman & Neuman (1953). It shows that in the infant animal almost the entire skeleton acts as a labile source of surface mineral, whereas in the adult, a very large part of the skeleton is metabolically inert. Any Mg in this inert part would not be available to maintain mineral homoeostasis by surface exchange. Undoubtedly, this state of affairs applies equally well to cattle. One explanation of the increased incidence of tetany in older cows as indicated by the calculations in Table 1 may well be that in them the magnesium of the skeleton is less readily available in times of dietary scarcity of the element or increased demands for it, and that their Mg-homoeostasis is impaired. An impaired ability of the skeleton of the adult to participate in exchange reactions probably accounts for the fact that chemical analysis of the bones of adult animals dying in tetany reveals little or no depletion of their Mg content (Cunningham, 1936a, b), whereas in young calves the bones may have lost 60% of their Mg (Blaxter & Sharman, 1955; Blaxter, 1955). Thus, Cunningham found the ash of normal adult bone to contain 0.42–0.64% Mg and the ash of bones of cows affected with hypomagnesaemic tetany to contain 0.45–0.67% Mg. In normal

calves the range is 0.55–0.75% Mg in the ash (Blaxter, 1955), and in deficient animals both under laboratory and field conditions the concentration of Mg falls to 0.17–0.45% of the ash. It may be pointed out at this juncture that Allcroft's (1947c) studies showed that seasonal hypomagnesaemias do not respond to Mg injections. After 24 hours the serum concentration returned to the low pre-injection level. The same is true of both the experimental and natural calf disease (Blaxter & Rook, 1955; Blaxter & Sharman, 1955). On the other hand, the data Allcroft presented show that the rapidly developing types of hypomagnesaemia in cows respond to a single injection of Mg and that the Mg of the serum remains within the normal range after the initial rise. When these results are considered in relation to results obtained with calves they certainly suggest that the two major types of hypomagnesaemia recognized by Green (1948) are those involving gross skeletal depletion and those involving but a temporary disturbance of skeletal homoeostasis. The rapidity of onset of clinical signs of tetany in the adult without depletion of bone Mg, compared with the slow development of the disease in calves with concomitant bone depletion, further suggests an impairment of skeletal homoeostasis of Mg in the adult animal.

It is of interest that in Forbes' complete lactation trials, previously referred to, in which he showed the cyclical nature of Ca metabolism in the cow, with losses of Ca occurring early in lactation and gains of body Ca in late lactation, Mg gains and losses tended to parallel those of Ca. Complete breakdown of the bone mineral to provide the Ca and P necessary for the maintenance of lactation evidently releases at the same time the Mg which is part of the crystal structure and this is then excreted. In considering the Mg homoeostasis of the bovine, one has to realize that Mg can be gained or lost by the bones without concomitant loss of Ca and P, but that large losses of Ca necessarily entail large losses of Mg as well. Furthermore, growth of soft tissues and augmented milk yields increase Mg demands while loss of flesh leads also to a small loss of Mg. It may be pointed out that there is no evidence from critical experimentation that the endocrine glands have any specific effect on Mg metabolism (Allcroft, 1947c).

THE MAGNESIUM CONTENT OF FOODS AND RATIONS

Mg is an essential element for plants, and many instances of Mg deficiency in crops have been noted in Great Britain, particularly following the heavy application of potassic fertilizers (Walsh & O'Donohue, 1945; Walsh & Clarke, 1945). As far as farm livestock is concerned, the data given in Tables 3 and 4 suggest that provided the concentration of Mg in the dry matter of plants and other foods exceeds 0.07% for growing stock and 0.1% for lactating cows, then little concern need be felt regarding an absolute dietary deficiency of the element.

Table 6, which has been compiled from a number of sources including our own analyses of a range of foodstuffs, indicates the average values to be expected on analysis of foods for Mg. These values are averages from a number of sources and can be very misleading if applied to

individual samples of foods since variation between samples is very wide.

TABLE 6

The magnesium content of some cattle foods*

Oil seeds and their products	Mg content on dry basis (%)
Linseed cake	0.48
Palm kernel cake	0.27
Proprietary concentrates	0.36
Cereal grains and cereal products	
Whole oats	0.09
Whole wheat	0.13
Whole maize	0.12
White rice	0.03
Wheat bran	0.51
Maize gluten feed	0.02
Wheat germ	0.34
Animal products	
Dried blood	0.02
Dried meat	0.03
Straws and hays	
Oat straw	0.10
Legume hays	0.30–0.60
Grass hays	0.15–0.30
Pasture grasses and herbage	
Clovers	0.69
Grasses	0.24
Herbs	0.75

* The analyses were taken from a variety of compiled sources – (see Mitchell & McClure, 1937; Orr, 1929; Thompson, 1953; Imperial Bureau of Animal Nutrition, 1936) together with analyses of feeding stuffs used in the metabolic trials referred to in the text.
The extent of possible variability is very high (see text).

Some generalizations are, however, possible. Firstly, the distribution of Mg in plant material tends to follow the distribution of P, rather than

that of Ca. Mg, unlike Ca, tends to accumulate in seeds, particularly oily seeds, and to be low in the leaves where Ca is usually high. It is also higher in tubers and roots than in the leaves. It is much higher in legumes, in fact, some samples of soya beans have contained as much as 1.0% of Mg. Animal products such as meat and blood meal and milk products are low in Mg and so, quite understandably, is maize gluten feed which is prepared by a washing procedure during the manufacture of maize starch. Forages such as straws and hays can vary widely in their Mg content, but their composition usually reflects the parent material, clover hays being much higher in Mg than grass hays.

TABLE 7

Effects of manuring with fertilizers containing nitrogen, potassium and magnesium on the Mg content of herbage dry matter

	Artifically dried herbage(1) Mg (%)	Spring pasture(2) Mg (%)	Pasture grass(3) Mg (%)
No manure	0.32	0.17	0.15–0.19
Nitrogen only	0.32	0.17	- - -
Potassium only	0.20	0.13	- - -
Magnesite + nitrogen	-	0.34	- - -
Magnesium limestone	-	-	0.25–0.31

(1) Stewart & Holmes (1953)
(2) Bartlett et al. (1954)
(3) Reith (1954)

Many soil and climatic factors are known to be responsible for very large variation in the Mg content of plants. Mg fertilizers increase the Mg content of herbage appreciably while potassic fertilizers result in considerable reductions in the Mg content. Instances of such effects are given in Table 7. High rainfall appears to be associated with a low Mg content of the dry matter, and drought with a high Mg content. Similarly, a high Ca content of the soil is usually associated with a low Mg content. Controlled experiments have shown for instance that by increasing the Ca content of the soil the Mg content of lucerne can be reduced from 0.67 to 0.14% (Hunter, 1949). A detailed account of the effects of manurial and other environmental factors on the Mg content of plants is given in a recent review by Krackenberger & Peterson (1954).

From Table 6, it is clear that some foods in common use may contain less than the minimal concentration of Mg necessary for the lactating

cow. Such foods, however, are never given as the sole ration and it seems very unlikely indeed that winter rations would fall below about 0.15% Mg on the dry basis (15–17 g./day) which is quite an adequate intake. Special conditions such as those in which Norwegian cows were given rations containing herring meal and fodder cellulose, both very low in Mg, are, of course, exceptions (Breirem et al., 1954). More normal rations of hay, purchased concentrates and roots would undoubtedly provide more than twice this quantity (28 g. daily). For spring grazing, however, some very low values for the Mg intake of the animal may be inferred. Allcroft (1954) and Bartlett et al. (1954) have found that on a field fertilized heavily with nitrogenous fertilizers, the Mg content of the herbage fell from 0.13% to 0.096% (0.22% MgO to 0.16% MgO) during the first few days of grazing. At this Institute, unpublished studies by the Grass and Dairy Husbandry Department show that pasture concentrations of Mg as low as 0.08% Mg occur in the spring and many samples of spring herbage fall in the range 0.08–0.12% Mg. In a series of hay crops grown on the Cockle Park plots in Northumberland, even lower values for Mg have recently been recorded, ranging from 0.06 to 0.15% (Thomas et al., 1955). These hay crops were also low in Ca and P. As shown by Bartlett et al. (1954) and by Reith (1954) Mg fertilization results in much higher concentration of Mg in the spring herbage (see Table 7).

It would appear reasonable to conclude, therefore, that in the spring, when cattle are turned out to grass, they can experience a decrease in their Mg intake compared with their intake on winter rations. At the same time, it is usual for an increase in milk yield and an improvement in body condition to occur. The cows' metabolism thus demands more Mg than it required before, but it often receives less. There is not necessarily an absolute deficiency of the element however; the adult disease cannot be regarded as a deficiency syndrome in the classical sense, firstly since its onset is so rapid, and secondly, because there is no indication of depletion of total bone Mg as there is in the calf disease which is a true nutritional deficiency.

These observations direct attention to the factors which might conceivably interfere with the normal methods whereby the cow adjusts her metabolism to fairly sudden changes in dietary intake and tissue requirements of the element.

SOME HYPOTHESES

There have been several attempts to provide explanations for the appearance of grass tetany in cows turned out to grass. Explanations have been sought in terms of the concomitant increases in the protein intake and in the K intake of the cow which take place at this time and in the changes which occur in the animal's acid-base equilibrium. The ground for these hypotheses appears to be the association of the disease with spring grass which is usually high in protein and K and sometimes posses-es an abnormal acid-base balance in its ash (Sjollema, 1952; Brouwer, 1952). Association does not imply causation, and direct experimentation

is necessary to find whether the association is fortuitous or not.

With K, experiments by Kunkel et al. (1953) purported to show that excessive K caused a slight reduction in serum Mg. This has not, however, been the experience of other workers carrying out similar experiments (Pearson, 1948; Pearson et al., 1949; Eaton & Avampato, 1952; Odell et al., 1952), and the single positive experiment of Kunkel et al. may be criticized since the effects of K were very small and could not be reversed by the addition of crude MgO. Our own experiments (Blaxter, Cowlishaw & Rook, unpublished) have shown that K intoxication in calves has no effect on the serum Mg, whether the calves are given adequate dietary Mg or not. Nor does K intoxication simulate the clinical syndrome of hypomagnesaemic tetany. The reverse experiment, in which K deficiency was produced (Blaxter, Cowlishaw & McGill, unpublished), also showed that no interference with Mg metabolism occurred.

With protein, the earlier work tended to incriminate toxic amines, notably guanidine, that might conceivably be formed during rumen fermentation. Later studies showed that guanidine was without effect on the blood Ca or Mg content (Shohl, 1939). Seekles & Sjollema (1932) provisionally incriminated nitrates, but their later experiments showed that nitrate poisoning produced an entirely different syndrome (Seekles & Sjollema, 1933).

Recently work at Reading has provisionally incriminated excessive ammonia formation in the rumen from fermentation of protein and other nitrogen-containing compounds of grass as a causative factor. It was found that the rise in serum urea was closely related to the incidence of hypomagnesaemia in groups of cows maintained on differently fertilized plots, and that ammonia evolution from grass was associated with hypomagnesaemia (Rook, 1954). Later work (Head & Rook, 1955) showed that in hypomagnesaemia developing on spring pasture, urine Mg excretion fell. A similar effect had been noted by Cunningham (1936b) who pointed out its association with the low serum concentration of the element. The fall in urine excretion observed by Head & Rook (1955) was, however, interpreted as due to a reduction in Mg absorption, and attempts were made to produce similar effects by dosage with ammonium salts. These caused a reduction in the urinary Mg excretion but no fall (Rook, 1954) or a slight fall (Head & Rook, 1955) in the serum Mg, the fall in urine secretion being interpreted as evidence of impaired Mg absorption. No direct estimate of Mg absorption necessitating estimation of the faecal loss of the element was, however, made. Usually less than 5% of the Mg ingested by cows is excreted in their urine, and experiments with small animals (see Shohl, 1939) show that changes in the routes of excretion of Ca and Mg can be induced by acid or alkaline diets without necessarily affecting their overall retention. It is possible that the decline in urinary Mg excretion without a concomitant fall in serum Mg was the result of an inability of the animal to excrete Mg in urine made alkaline by excessive ammonia excretion. Even if ammonia production from spring grass blocked absorption of Mg completely, an explanation is still needed of the apparent

inability of the cow to utilize the mineral reserves of her bones in the way in which the young animal experimentally placed in a similar predicament is able to do.

A reinterpretation of Sjollema's (1931) analyses of the Dutch pastures producing tetany was made by Brouwer (1952). He showed that pastures which cause tetany in cows have a high "alkali alkalinity" and an extremely low "alkali earth alkalinity" compared with normal grazing. The former is defined as the algebraic sum in terms of mg. equivalents (K + Na – Cl – S) and the latter by the similar algebraic sum (Ca + Mg – P). Brouwer ascribed the major cause of these changes to the high K content of the herbage. Whether the changes in acid-base equilibrium of the animal, which might well occur under such conditions, are responsible for the disorder is not known.

CONCLUSIONS

From the data reviewed it appears that the Mg requirement of cattle is usually met by the feeds with which they are supplied. Exceptions do, however, occur. In the calf reared on whole milk the diet does not supply enough Mg and, after a long period in which the serum Mg slowly falls, tetany occurs. The bones of these animals are depleted of Mg and the condition may be regarded as a true dietary deficiency. The response of the serum Mg to Mg injection is temporary. It also appears that in Norwegian cows, maintained for long periods on rations of fodder cellulose, the tetany which eventually occurs arises from a dietary lack of Mg, or a low availability of the Mg of these foods. This is also the opinion of the Norwegian workers themselves and of Dutch authorities on the condition, but critical confirmatory evidence from bone analyses and the response of serum Mg to single injections of the element is not available. Some of the slowly developing seasonal hypomagnesaemias may arise in the same way.

The hypomagnesaemia of the adult cow occurring relatively suddenly when cows are turned out to pasture in the spring cannot be regarded as a dietary deficiency of the element in the classical sense. It is too rapid in occurrence, there is no gross depletion of the total Mg of the bone, spontaneous remission often occurs without change of diet and the response to a single injection of Mg is usually complete. Such changes in management often involve sudden increases in metabolic demands for Mg and often a fall in intake, early spring grass usually being low in Mg concentration. It can be inferred that Mg homoeostasis is impaired, and the data reviewed suggest that in animals which develop tetany the normal process of heterionic exchange of the element at the bone crystal surface is at fault. The hypothesis that excess K in spring grass interferes with Mg metabolism has been shown to be untenable, while the hypothesis that non-absorption of the Mg of grass possibly due to the formation of ammonium complexes in the digestive tract, even if correct, still leaves unanswered the problem of why the lactating cow cannot release Mg from her bone mineral in the face of a low absorption from her digestive tract.

Further experimentation is required to elucidate the marked differences in the reactions of the young as compared with the adult bovine animal to changes in its Mg requirement and supply. The differences may prove to be attributable (a) to age changes in the proportion of the skeletal Mg present at the crystal surfaces, (b) to age changes in the rate of recrystallization of bone or (c) to dietetic and environmental fluctuations engendering changes in the ionic composition and acid-base equilibrium in the extracellular fluid surrounding the bone crystal.

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Lead Poisoning in Animals

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Though the more obvious forms of lead poisoning in animals have been recognized and diagnosed clinically and chemically for a very long time, more recent work has shown that the toxic effects of lead are a factor in the ill health or death of a much wider range and a far greater number of animals than was realized about 10 or 15 years ago.

Heslop (1925) must have suspected this possibility when he made a plea for finding the significance of the levels of lead in the tissues of normal and lead-poisoned animals. Fortunately about that time Fischer (1925) introduced the reagent "dithizone" which made the determination of the micro amounts of lead found in tissues, even in poisoning, practicable and convenient.

Shrewsbury et al. (1945), while investigating a long standing difficulty in rearing calves from beef cows and heifers, suspected that the calves might be obtaining a toxic material when they were observed chewing the corral fence. Following this line they correlated abnormal levels of lead in the liver of affected calves with muscular tremors, partial or complete blindness, staggering and convulsions, and death. They reproduced the condition experimentally by feeding lead acetate and carbonate. This work, which proved that lead toxicosis could occur in calves without causing severe lesions in the alimentary tract, stimulated interest in the whole question of low grade lead poisoning in cattle. This was a great advance in the whole subject, since most previously reported cases of poisoning in cattle had been associated with large intakes of lead compounds from the chewing of old paint pots, lumps of red lead in oil, painted tarpaulins, or broken batteries. Generally in these cases inflammation of the abomasum has been typical. Systematic dosing of paint flakes to calves was done by White & Cotchin (1948) and this work yielded factual data on the levels of white lead necessary to produce death in these animals.

From results obtained in their diagnostic work Fenstermacher et al. (1946) suggested diagnostic criteria based on the analysis of a number of livers from cases of suspected lead poisoning in cattle. They considered that up to 3 p.p.m. of lead in wet liver were of no significance, that 5 p.p.m. should be regarded with considerable suspicion and 10 p.p.m. as positive evidence of lead in lethal amounts. Experience gained at Wallaceville on some hundreds of cases confirms that these figures form a very good basis for diagnosis on biochemical grounds, whether or not supporting clinical evidence is forthcoming.

The critical work of Blaxter & Allcroft (1950), involving the dosing of various lead compounds to sheep and cattle, and the analysis of faeces, urine, milk, blood, kidneys, liver, and other tissues, was a significant contribution to the understanding of lead poisoning in ruminants. They laid down slightly more conservative chemical criteria for the diagnosis of poisoning, but at Wallaceville it is considered that their levels are too high and that this would sometimes result in failure to diagnose correctly true cases of lead poisoning. It was also demonstrated that cumulative lead poisoning in ruminants is virtually non-existent (Allcroft, 1951). Their findings in the diagnostic field, coupled with those of other workers, have indicated the widespread occurrence of lead poisoning in ruminants and it is likely that even now only a small proportion of the deaths from lead poisoning are correctly diagnosed or in fact even suspected.

Though the Weybridge work indicated that metallic lead given as shot or dust is not toxic to calves, not everyone will agree that this is the final word on the toxicity of the metal. Too many field cases of lead poisoning in ruminants can be cited where metallic lead, possibly as an alloy, has apparently been the only source. Further work is needed to determine the influence of other metals in lead alloys on the rate of solution and absorption of the lead in ruminants.

Following earlier work on lead poisoning in dogs by Mitchell (1940), Lieberman (1948), Bond & Kubin (1949) and others, Staples (1955) has produced both acute and chronic poisoning experimentally using basic lead carbonate (white lead). Lead levels in blood and liver were determined. Concurrently with the experimental work, about 50 cases of lead poisoning in dogs have been diagnosed at Wallaceville, mainly on biochemical grounds, but usually with an associated clinical picture of damage to the central nervous system. In most of the cases no clear evidence of the source of lead was obtained, but occasionally there was a history of painting being done in the vicinity and in one case a dog was being watered from an old paint tin. Many of the cases were sent in with a tentative diagnosis of post-distemper encephalitis, canine virus hepatitis (Rubarth's disease), or canine hysteria. Some cases had clinical canine virus hepatitis and sufficient lead in the liver to warrant diagnosis of lead poisoning. Further work on the interaction of lead and infectious diseases in dogs is required. Perhaps as in man infectious disease causes a rapid and dangerous mobilization of lead deposited in bone. It is not clear whether dogs are like cattle in seeking out and eating lead compounds or whether they ingest lead involuntarily through playing with sticks that have been used for stirring paint or through gnawing at lead painted woodwork.

The lead hazard also extends to animals and birds in zoos and to laboratory experimental animals. In New Zealand fatal lead poisoning has been diagnosed in a polar bear, a kra monkey, lorikeets and ferrets. The ferrets had haemolytic jaundice but no clinical signs of involvement of the central nervous system. The others all had cerebral symptoms. In each case paintwork containing lead was accessible to the animals and birds.

The treatment of acute lead poisoning in ruminants has always been difficult owing to the rapidity of death after the appearance of nervous symptoms. In calves death may occur as quickly as an hour after convulsions appear. Before their appearance there is often little to indicate that lead poisoning has occurred.

Treatment requires a suitable drug and the ability to reach a diagnosis early enough for effective use of the drug. No really adequate drug is yet available though there is distinct promise in calcium disodium ethylene diamine tetraacetate which Holm et al. (1953) have found to be effective in the treatment of experimentally induced acute lead poisoning of calves and natural chronic poisoning of horses. The salt is harmless to dogs also, in therapeutic doses, and further work on experimental and natural cases of lead poisoning is fully merited. It might be of special value for chronic lead poisoning in dogs, which is not infrequent and which can be presumed if the blood contains above 1.0 p.p.m. of lead (Staples, 1955). If the drug maintains its promise when more widely studied, it will be a most valuable addition in therapy.

In the diagnosis of lead poisoning, especially in cattle, the problem is the absence of clearly defined symptoms until the terminal convulsive phase. The first warning is usually the finding of a dead animal or one showing cerebral symptoms in circumstances in which it is evident that lead has been ingested. The problem is what to do about the remaining animals that have had access to the lead. Allcroft (1951) has shown that analysis of blood and faeces from the living animal may assist in diagnosis and prognosis. High levels of lead in both blood and faeces indicate recent ingestion of lead and the possibility of progress of the disease; a high level in blood and a low level in faeces indicates that lead has not been ingested recently and that the animal has a better chance of survival even without treatment. The delay whilst analytical work is carried out may be safe for adult animals but would be extremely unsafe for calves as it is the habit of young calves to imitate others in chewing or sucking fences and walls. It is commonly found that when one of a mob of calves dies from lead poisoning, others will die over the ensuing few days, even though they may not have symptoms at the time of the first death. The veterinary practitioner, having considered the circumstances, would probably decide to treat all the calves which had had access to lead and then, where analysis of blood and faeces was possible, to continue treatment of those which the analytical evidence indicated had ingested lead.

In view of the difficulty of differentiating clinically and histologically between lead poisoning and many diseases involving the central nervous system, chemical examination for lead in animals having any access to this material or exhibiting cerebral symptoms will often throw light on otherwise obscure conditions.

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